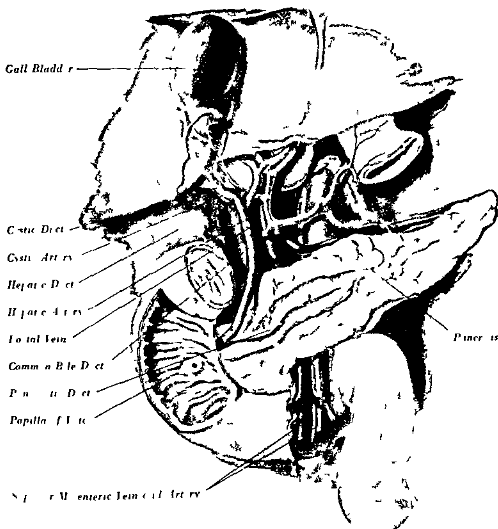
PLATE I



A t i el it n hip of extra patic bile duct to ontig u t tur s (Courte y of S umar Sharp and Doh n)

Practical Management of Disorders of the LIVER, PANCREAS, AND BILIARY TRACT

BY

JOHN RUSSELL TWISS, M.D., F.A.C.P.

Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School; Attending Physician, University Hospital; Assistant Visiting Physician, Fourth Medical Division, Bellevue Hospital

AND

ELLIOT OPPENHEIM, M.D., F.A.C.P.

Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School; Associate Attending Physician, University Hospital; Assistant Visiting Physician, Fourth Medical Division, Bellevue Hospital

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THIS BOOK IS DEDICATED

TO THE MEMORY OF

DR. R. FRANKLIN CARTER

A BELOVED FRIEND, ASSOCIATE, AND TEACHER

CONTRIBUTORS

Samuel L. Beranbaum, M.D.
Associate Clinical Professor of Radiology, New York University Post Graduate Medical School

William V. Berger, M.D.
Assistant Clinical Professor of Medicine, New York University Post Graduate Medical School; Assistant Visiting Physician, Fourth Medical Division, Bellevue Hospital; Formerly Professor of Medicine, University of Graz

Frederick J. Brady, M.D.
International Health Representative, Division of International Health, Public Health Service, Federal Security Agency

Maurice Bruger, M.D., C.M., F.A.C.P.
Associate Professor of Medicine, New York University Post Graduate Medical School; Chief, Department of Clinical Pathology, and Attending Physician, University Hospital; Visiting Physician, Fourth Medical Division, Bellevue Hospital

Charles O. Fiertz, M.D.
Assistant in Neurology, University Hospital

John Cazzola, M.D.
Formerly Assistant in Surgery, University Hospital

Alexander S. Honig, M.D.
Assistant in Medicine, University Hospital

Willard H. Wright, Ph.D., D.V.M.
Chief, Laboratory of Tropical Diseases, National Microbiological Institute, National Institutes of Health, Public Health Service, Federal Security Agency

FOREWORD

This volume by Dr Twiss and Dr Oppenheim and their collaborators represents the outgrowth of years of inquiry on problems dealing with sundry disturbances of the upper digestive tract At the Combined Medical and Surgical Biliary Tract Clinic at the old Post Graduate Hospital in New York City studies were initiated by the late Dr R Franklin Carter which have evolved through the years into an ever enlarging field of physiologic and clinical knowledge He and his co-workers including several of the authors were among the first to recognize and characterize certain functional disorders of the biliary tract They explored the usefulness of biliary drainage and the examination of bile as practical diagnostic procedures They compiled their case records thoroughly and thoughtfully and were thereby equipped to challenge and modify many of the time honored dogmas which had been entrenched in the literature From this vast store of personally collected quantitative data come the portions of this book which will no doubt be of greatest interest to students in the field

The rapid advances in the biologic sciences have brought to light four hundred or more activities ascribable to the liver alone The mechanisms upon which metabolic and excretory processes depend are unknown or at best are highly speculative at the present time No treatise on the liver or pancreas or biliary tract dealing with normal functions or derangement patterns in disease can be entirely satisfactory while so much remains at the descriptive level The authors recognize the futility of attempting to satisfy all types of readers when dealing with topics so vast and very wisely focus their efforts on clinical usefulness and on transcribing the best available current opinions Practicing physicians especially those in need of concise information and authoritative references should appreciate how well they have succeeded

Franklin M Hanger M D
Professor of Medicine Columbia University College of Physicians and Surgeons

PREFACE

The purpose of this volume is to furnish a practical guide in the diagnosis and management of those disorders of the liver, pancreas, and biliary tract most commonly encountered in medical practice. No attempt has been made to be encyclopedic. Rather, our aim has been to present brief and concise information which is readily available and applicable to everyday medical problems. Certain subjects are dealt with in more detail than are others. This has been done where the material is of great practical importance, in subjects where our experience has been particularly wide, or where, in our opinion, the subject matter is not generally available in other textbooks.

The bases of the personal experiences upon which this book is founded are primarily those of the private practice, clinic, and hospital work of the physicians and surgeons of the combined Medical and Surgical Biliary Tract Clinic of the New York University Hospital (formerly the New York Post Graduate Hospital). The clinic was founded in 1929 by Dr. R. Franklin Carter, who served continuously as its director for twenty-three years. During the ten years preceding the writing of this book, almost five thousand duodenal drainages were performed.

The general acceptance of the material used in clinical practice and its proved value in post graduate teaching justify, we believe, publication of these data in permanent form. Some of the material has been presented previously in conventions and medical meetings.

For purposes of organization, the disorders of the gallbladder and extrahepatic ducts are considered in one section, and those of the liver and pancreas in separate sections. Clinically, however, they must be integrated. Disorders of the liver have their effect on the pancreas, gallbladder, and bile ducts, and vice versa. With this in mind, a fundamental purpose of our presentation has been to facilitate and to correlate diagnostic procedures and appropriate methods of management to attain specific diagnoses and to utilize as far as possible the indicated specific forms of treatment. Medical therapy is discussed in considerable detail. Surgical therapy is concerned with principles and indications for operation rather than with details as to surgical procedure.

In the preparation of the text we have drawn freely from the experiences of our associates and also from the literature For those who wish further details in any subject there are bibliographies at the end of each chapter The final section of the book gives detailed instructions as to diagnostic procedures and diets

We are indebted to the late Doctor Carter for his advice in the preparation of the text and for the use of clinical material and illustrations Most of the illustrations not credited to others were furnished by Doctor Carter We are also indebted for a review of parts of the text to many of our associates particularly Doctors Lee Gillette Jere W Lord Jr Maurice Bruger, M N Richter and Louis Rousselot For the tedious job of typing the manuscript our thanks to Mrs Mary Nicklo and the Misses Frances Beach and Jeanne Walter We are also indebted to Mrs Nicklo and Miss Helen Member for fifteen years the Clinic Secretary for aid in preparing the text for publication

While every effort has been made to present the most significant pertinent data relative to the clinical management of the disorders discussed errors and oversights are inevitable because of the vast amount of material published on these subjects For omissions of this character we ask the indulgence of our readers We would appreciate suggestions as to addition or corrections

We also wish to thank our publishers for the help advice and assistance so freely given in the preparation of the book Finally we offer our heart felt thanks to our long suffering wives without whose consideration and understanding this book could not have been written

J R T
E O

New York N Y

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Section I

Chapter 1

HISTORY AND PHYSICAL EXAMINATION

THE HISTORY

Since a well-taken history is an essential part of the diagnostic investigation, a review of procedures seems merited.

The Chief Complaints.—Pain is the chief complaint of most patients with gall bladder disorders; pain may also be a prominent feature of those with liver disease. An intolerance to roughage and foods high in fat is frequent. Occasionally there is an apparent allergic reaction to certain foods.

The usual symptomatology of chronic liver disease not associated with pain or with gall bladder disease is deserving of a brief review. Generally speaking, the symptoms which may be found with chronic liver disorders are headache, anorexia, nausea, discomfort after meals, bad breath, coated tongue, constipation or diarrhea, epigastric or right upper quadrant pain or tenderness, and mental depression. With more advanced disease there may be epistaxis, hematemesis, melena, emaciation, cachexia, enlargement of the abdomen, ankle edema, cerebral symptoms, coma or death. Any of the above symptoms indicates the need of a detailed history, especially in regard to the use of alcohol, starvation, cardiac disease, or exposure to hepatotoxic materials. Occupational hazard or dietary factors which might have contributed to the involvement of the liver should also be kept in mind. Details can be found in the various chapters on these subjects.

The early diagnosis of acute liver disease is discussed on page 273. *Acute yellow atrophy* or acute necrosis of the liver (p. 280) is deserving of mention because of its abrupt onset and frequently rapidly lethal clinical course. *Chronic pancreatitis* may give intermittent attacks of abdominal pain, epigastric or left upper quadrant in location. These symptoms are discussed in detail in diseases of the pancreas (p. 416). The symptoms of chronic liver disease are described on page 279. Hemorrhage is one of the more serious and frequently terminal events in *cirrhosis of the liver*. (See p. 300.) It may be evidenced by nosebleed, vomited blood, or tarry stools.

Pain.—*Character.* Pain may be dull, colicky, aching, constant or intermittent. Colicky pains are most apt to occur as the result of the sudden overdistention of the biliary tract caused, for example, by an impacted stone or by a spastic common-duct sphincter. A dull, constant, prolonged type of pain may be produced by a gradual distention of the

biliary tract such as that resulting from a fibrotic or neoplastic common duct stricture. A constant type of pain may also occur as the result of neoplastic or inflammatory conditions of the gall bladder, liver or pancreas.

Intrahepatic pain is usually referred to the epigastrium or right upper quadrant with radiation to the back. The character is usually aching; however, it may become severe with overdistention of Glisson's capsule. The enlarged liver of extrahepatic biliary tract obstruction is seldom very painful unless it is associated with active infection.

Onset.—The onset of biliary tract pain commonly occurs several hours after a heavy meal, particularly one rich in fats. Pancreatic or liver pain may occur after alcoholic excesses. The ingestion of roughage may precipitate attacks, especially in those having gastric hyperacidity or duodenitis. Colic, on the other hand, may occur for no particular reason. It can and frequently does waken the patient out of a sound sleep.

Frequency.—Frequently recurring attacks of pain, particularly if severe, suggest the need of surgical intervention. The intervals between attacks of pain should always be noted.

Location.—Pain occurs with equal frequency in the epigastrium and in the right upper quadrant in proved gall bladder disease. The pain of liver disease is more commonly in the right upper quadrant; it may, however, occur in the epigastrium.

Radiation.—The pain of gall bladder disorders often radiates to the back, especially to the region of the right scapula. With diaphragmatic irritation there may be pain in the shoulder or difficulty in breathing. Radiation to the precordial region may occur with overdistention of the common or cystic ducts. Generalized pain of the upper abdomen may occur. The pain of pancreatic disease may be boring in type and localized in the epigastrium or the left upper quadrant. The pain may radiate directly to the left lumbar region, the precordium, or the left lower quadrant.

Duration.—Pains of short duration may be functional in origin, particularly if relieved by nitroglycerin, amyl nitrite or intravenous aminophyllin. Attacks severe enough to require opiates for relief may be assumed to be organic in origin.

Aggravating Factors.—Pains originating in the biliary tract may be aggravated by food high in fat, as well as by irritating types of foods such as sauces, condiments or roughage. Similar effects may result from nervous tension, worry, excitement, or undue fatigue.

Means of Relief.—The means of relieving biliary tract pain consists of antispasmodics, narcotics and heat. The persistent pain of an overdistended biliary tract owing to a hypertonic dyskinesia may be relieved by a bland diet. Pain associated with gastric hyperacidity or duodenitis responds well to antacids. Symptoms of the postcholecystectomy syndrome are discussed on page 196. The interval between the onset of acute pain and jaundice is of interest. With lower common duct obstruction associated with the absence of the gall bladder or cystic-duct obstruction, jaundice follows pain within twelve hours. With a functioning gall bladder, however, the onset of jaundice may be delayed three or four days. For a detailed discussion of jaundice, see Chapter 19, pages 365 to 378.

ASSOCIATED SYMPTOMS

Loss of weight may occur with advanced organic disease of the pancreas liver or extrahepatic biliary tract Loss of strength anorexia cachexia and anemia may also occur especially with malignancy or cirrhosis of the liver A preceding alcoholic history with concomitant abdominal enlargement ascites edema or hemorrhage suggests cirrhosis In this clinic however the most common cause of loss of weight is chronic cholecystitis With this condition the patient usually volunteers the information that she is afraid to eat

Constipation is one of the most frequent symptoms associated with chronic disease of the biliary tract Its presence in the aged and in those with a spastic irritable colon has been mentioned

The *past history* should especially note recurrent digestive attacks which indicate chronic disease of long standing Furthermore the presence of other foci of infection may be of significance especially those in the sinuses tonsils teeth appendix and urinary tract

A review of *past illnesses* and *operations* may give information having a direct bearing on the presenting symptoms An arthritis of the spine for example may be responsible for recurrent attacks of pain in the right or left upper quadrants Chronic heart or renal diseases may also give pain or other digestive symptoms simulating biliary tract disease The frequent association of organic disease of the gall bladder liver and heart should always be kept in mind

A *systemic review* of the usual type concerning the gastro-intestinal cardiovascular respiratory and genitourinary systems may also give information having a bearing on the digestive symptom The well known relationship of symptoms suggesting biliary tract disease to other systems is discussed in the appropriate sections (See p 217)

The *family history* may be of interest in relation to longevity and disease of parents and siblings The possible relationship of jaundice arthritis hypertension or neoplastic disease afford at times leads of value

The immediate family of the patient is of even greater importance especially in regard to the health and compatibility of the marital partner Lack of proper sexual or social adjustment frequently leads to digestive disorders as do a multitude of other situations relative to the family Financial worries and responsibilities which either partner is unwilling or unable to meet form common sources of difficulty Physically or mentally inadequate children may also cause digestive symptoms in the parents

The *personal history* should include a review of the patient s occupation his attitude and adjustment to his work his financial compensation and possible incompatibility with his associates or superiors Problems here may be responsible for digestive symptoms

Dietary and hygienic habits should be reviewed as excessive smoking and alcoholic intake may play an important part in producing digestive symptoms Furthermore the same result may be obtained from the excessive use of irritating types of foods such as condiments sauces spices or salted food Digestive disorders may also result from irregular eating habits such as skipped or delayed meals eating when nervous or unduly

TABLE 1.—BILIARY TRACT CLINIC

DATE
NAME
ADDRESS
OCCUPATION

AGE SEX
S M W D
REFERRED BY

CHART NO
NATIONALITY
W B

C C *D*
Pain
Char

1st Attack
Last Attack
Freq
Duration
Hypo Req
Onset
Location
Radiation
Aggrav by
Relieved by

Associated Symptoms
Jaundice
Nausea
Vomiting
Belching
Distention
Fat Intol
Loss of Wt

Headache
Fever
Chills
Tender R U Q
Clay Col Stool

Symptoms between Attacks

P I (To be recorded reverse side)
A Details not covered above
B Previous treatment
C Results of treatment
D Transfusions
Blood or Plasma

F H
Children—No
Ages
Misc
Fam Hist

P H
Illnesses
Operations

Resp
C V
C I
Const
Mucus Blood
G U
Ment N N

Previous Examinations
Date
X ray
Blood Chem
G B Drg
Other

Physical Exam
Ht Wt
B P T P R

Appear

Norm Sthenic Asth
Head
Eyes
N & T
Heart
Lungs
Abdomen
Tenderness
Palp Liver
Palp Spleen

Extrem
Reflexes

Tentative Diagnosis

Assoc Conditions

Final Diagnosis

Advise Date
X ray
Duod Drg
Blood Chem
Other
Hosp Adm
Follow up

fatigued bolting of food or the resumption of mental or physical labor immediately after a meal

A common sense correction of any detrimental habits or situations having an apparent adverse effect may be far more efficacious than drugs in the relief of symptoms

The summary chart of the diagnostic investigation used in our clinic is shown in Table 1

THE PHYSICAL EXAMINATION

The primary consideration in the physical examination of the patient having symptoms of biliary tract disease should be a detailed investigation to determine the presence of any systemic disease which might be responsible for the presenting symptoms

The initial recorded findings should include the patient's age height weight temperature and blood pressure Under the age of forty there is a different group of diseases from that in patients over forty Younger patients are more susceptible to the functional disorders and the acute inflammatory diseases of the liver whereas the older group show more frequent cholelithiasis cirrhosis and malignancy The weight of the patient should be compared with normal standards A recent change in weight is usually significant The recorded temperature may reveal the presence of inflammatory conditions which otherwise might not have been suspected The blood pressure likewise may vary considerably from hypotension (which may be associated with asthenia or adrenal disease) to hypertension commonly found in elderly patients

The general appearance should be noted Common findings of internal tension are dilated pupils excessive posterior cervical tenderness a spastic tender colon cold clammy hands and overactive reflexes Nutritional disturbances may show as weight loss anemia or cachexia Jaundice is sometimes overlooked in artificial light Abdominal examination may reveal enlargement vascular disturbances as collateral circulatory changes or edema Abnormalities in posture may indicate arthritis The older cachetic patient with a drawn hepatic facies and a protuberant abdomen full of fluid is significant of cirrhosis

A history of recurrent colds sinusitis or sore throats justifies a detailed nose and throat examination Dental caries or suspicious teeth justify a similar investigation A rectal and if necessary a proctosigmoidoscopic examination may reveal evidence of rectal prostatic or colonic pathology

A careful examination of the skin may reveal evidence of biliary tract disease The facies may show multiple dilated venules or spider angiomas (Fig 1) The upper lids may show the yellowish plaques of cholesterol known as xanthelasma palpebrarum Similar masses are sometimes found in the creases of the palms of the hands (*xanthoma planum*) or as nodular lesions of the elbows (*xanthoma tuberosum*) These lesions may occur with hypercholesterolemia xanthomatous biliary cirrhosis or diabetes mellitus The slate-colored jaundiced appearance of hemochromatosis should also be mentioned Evidence of collateral circulation may be found in the dilated veins

TABLE 1 —BILIARY TRACT CLINIC

DATE
NAME
ADDRESS
OCCUPATION

AGE SEX
S M W D
REFERRED BY

CHART NO
NATIONALITY
W B

C C D r

Pain
Char

1st Attack
Last Attack
Freq
Duration
Hypo Req
Onset
Location
Radiation
Aggrav by
Relieved by

Associated Symptoms

Jaundice	
Nausea	Headache
Vomiting	Fever
Belching	Chills
Distention	Tender R U Q
Fat Intol	Clay Col Stool
Loss of Wt	

Symptoms between Attacks

P I (To be recorded reverse side)
A Details not covered above
B Previous treatment
C Results of treatment
D Transfusions
Blood or Plasma

F H
Children—No
Age
Misc
Fam Hist

P H
Illnesses

Operations

Resp

C V

G I

Const

Mucus Blood

G U

Menst N N

Previous Examinations

	Date
X ray	
Blood Chem	
G B Dye	
Other	

Physical Exam
Ht Wt
B P T R

Appear

Norm Sthenic Asth
Head
Eyes
N E T
Heart
Lungs
Abdomen
Tenderness
Palp Liver
Palp Spleen

Extrem
Reflexes

Tentative Diagnosis

Assoc Conditions

Final Diagnosis

Advice	Date
X ray	
Duod Drg	
Blood Chem	
Other	
Hosp Adm	
Follow up	

PLATE II



Xanthomatous infiltrations A Yellowish red lesions on the extensor surface of the forearms B Localization in the creases of the fingers C Xanthelasma D Xanthoma diabeticorum E Xanthoma tuberosum lesions are common on joints and in the tendon sheaths (Lewis G M Practical Dermatology p 238 plate 87 W B Saunders 1952)



Fig 1 —Spider angioma

Fig 2 —Collateral circulation of the distended abdominal wall showing the dilated veins by infra red photography

of the thorax or abdomen (Fig 2) Hemorrhages occur at times subcutaneously or from the mucous membranes in patients deficient in prothrombin On the legs there may be purpuric rashes varicose veins or varicose dermatitis

Examination of the neck may reveal enlarged nodes which are sometimes of metastatic origin Biopsy of such a gland may yield valuable information

The chest should be examined for evidence of any pathologic condition of the heart and lungs Careful inspection and palpation of the breasts is essential The absence of chest hair and presence of gynecomastia is sometimes found in males with cirrhosis of the liver The axillae should be palpated Roentgen ray study is indicated in all questionable cases especially where pulmonary tuberculosis metastases fluid effusion or organic disease of the heart is suspected

Abdominal examination may reveal ascites hepatomegaly splenomegaly or pancreatic cysts Abdominal masses should be differentiated from the diffuse enlargement due to ascitic fluid

Among the causes for an enlarged liver French* has listed the following

- Venous congestion—cardiac cirrhosis
- Obstruction of common bile duct
- Suppuration of liver—multiple abscesses
- Cirrhosis of the liver
- Splenic anemia (Banti's syndrome)
- Hemochromatosis (bronzed diabetes)
- Syphilis of the liver
- Chronic perihepatitis
- Carcinoma of the liver—primary or secondary
- Sarcoma of the liver
- Fatty liver
- Lardaceous liver
- Polycystic liver

Fluid if present in large amounts usually gives a generalized abdominal enlargement with bulging of the dependent parts in the prone or upright positions With an appreciable amount of abdominal fluid there are usually a fluid wave flatness in the flanks on lying down and shifting dullness on change of position The liver may be ballotable giving a bouncing sensation on deep pressure There may be edema of the legs or scrotum with or without ascites French has summarized the various causes of ascites and enlargement of the spleen

With an apparent splenomegaly French states that the following possibilities should be considered in differential diagnosis

- Kidney tumors
  - Perinephritic inflammation or abscess
- Suprarenal tumors
- Carcinoma splenic flexure of colon
- Pancreatic tumors
  - Cysts carcinoma
- Gastric neoplasms
- Ovarian tumor
- Tuberculous peritonitis
- Fecal masses of colon

* French H *Differential Diagnosis* 6th ed Baltimore Wood p 471 1945

pable gall bladder should be mentioned hydrops and empyema of the gall bladder Malignancy of the gall bladder may give a palpable mass in the right upper quadrant The palpable Courvoisier gall bladder is usually due to stricture inflammation or malignancy involving the head of the pancreas or the common bile duct

A tender mass in the region of the gall bladder may be due to an acute cholecystitis In these patients there is commonly a prolonged history of recurrent indigestion because of the presence of a chronic cholecystitis and cholelithiasis The elderly patient with a gangrenous gall bladder may have acute tenderness without fever or leukocytosis

Splenomegaly may occur with cirrhosis of the liver as the result of portal hypertension Other causes of splenomegaly should be ruled out There may be associated hepatomegaly ascites and varicosities of the esophagus or other parts of the gastro-intestinal tract

The physical findings in the patient with jaundice may be of assistance in differential diagnosis In hemolytic prehepatic jaundice the icterus is not pronounced and there may be splenomegaly The diagnosis of this condition is discussed in detail on pages 373 to 374

With acute hepatic types of jaundice enlargement and tenderness of the liver are common (See p 374) In chronic types of hepatic jaundice there may be both hepatomegaly and splenomegaly *i e* cirrhosis (See p 374) With acute hemorrhage pancreatic necrosis shock cyanosis and tenderness over the gall bladder and pancreas are prominent features

Occasionally children are seen with jaundice or hepatic enlargement Excluding the transient icterus neonatorum jaundice in the newborn is usually caused by some obstruction of the biliary tract such as congenital absence of the biliary ducts intra or extrahepatic stricture cystic diseases of the common duct or rarely by the presence of inspissated mucus Cirrhosis may also occur in young children

With the jaundice due to congenital syphilis there may be a hepatomegaly snuffles and later Hutchinson s teeth and interstitial keratitis Jaundice may al o be associated with enlargement of the liver secondary to malignancies which are sometimes retroperitoneal in origin Among other causes of jaundice to be considered are blood dyscrasias Pick s disease or adhesive pericarditis may be associated with generalized edema

An excellent review of physical findings in diseases of the liver gall bladder and pancreas has been published recently by Butler and Bargen *

In summary the carefully taken history and a complete physical examination should serve as the basis for a tentative diagnosis This diagnostic impression in turn indicates the type of laboratory and roentgen ray studies which are necessary to confirm the diagnosis

Butler D B and Bargen J A Abdominal Masses in Diseases of the Liver Pancreas and Spleen Gastroenterology *19* 32 1951

French* lists the following possibilities as etiologic factors in splenomegaly

A Spleen greatly enlarged

Leukemia	Gaucher s disease
Malaria	Still s disease
Polycythemia	Familial acholuric jaundice
Splenic anemia	Schistosomiasis

B Spleen moderately enlarged

Pernicious anemia	Typhoid fever
Rickets	Relapsing fever
Congenital syphilis	Typhus
Cirrhosis of the liver	Septicemia
Portal hypertension	Embolism

Frequently a satisfactory abdominal examination is impossible without a paracentesis The fluid removed is of great value in differential diagnosis and should have a detailed laboratory investigation Exudate fluid hemorrhagic or otherwise abnormal in appearance may be obtained in malignancies and in other pathologic conditions

A detailed study of the liver should be recorded at the time of the initial examination A palpable liver is not necessarily enlarged a ptosis may be present Enlargement is noted as being localized or diffuse The consistency of the liver is described The smooth enlargement of the liver adjacent to the gall bladder found with Riedel s lobe should not be considered a pathologic finding

In early stage of liver disease there may be found a diffusely enlarged fatty liver The enlarged soft and frequently tender liver may be found in acute or chronic parenchymal disease of this organ or in cases of extrahepatic biliary obstruction The hard nodular liver suggests cirrhosis or malignancy

Tenderness of the liver associated with chills and fever indicates active inflammation Localized masses may be found with malignancies abscesses or cyst Malignancies are usually secondary to a primary lesion elsewhere in the gastro intestinal or biliary tract

Among the less common causes of liver disease are parasitic infections Cirrhosis may be due to schistosomiasis in countries where this disease is prevalent Biliary tract obstruction may occur with this condition or with worms from the gastro-intestinal tract such as *Ascaris lumbricoides* Hydatid cysts or amebic abscess may occur in the liver

The size of the liver should be carefully noted daily in the acutely ill patient since acute necrosis may supervene in almost any type of liver disease An actual diminution in size within a few days may be demonstrated by palpation and percussion in these patients

In the chronically ill patient the diseased gall bladder is seldom enlarged or palpable preoperatively Among the causes of an enlarged gal

French H *Differential Diagnosis* 6th ed Baltimore Wood p 769 1945

Section II

Disorders of the Gall Bladder and Extrahepatic Biliary Tract

Chapter 2

BASIC FACTORS—ANATOMY, PHYSIOLOGY AND BACTERIOLOGY OF EXTRAHEPATIC DUCTS

ANATOMY

THE gall bladder with the cystic duct may be looked upon as a diverticulum of the bile duct enlarged at its extremity to form a reservoir for the bile. It is normally absent in animals such as the horse, deer, rat, pocket gopher, dove and peccary. Complete absence in the human is rare. The fact that for years after operative removal of the gall bladder many people enjoy healthy life does not prove that the gall bladder is a rudimentary organ. If this were so, states Aschoff,[1] one would also have to designate the spleen, half the stomach or large intestine, and even the arm and leg as rudimentary organs.

The gall bladder lies obliquely on the inferior surface of the liver and is usually pear shaped. The wide end or fundus usually reaches the anterior border of the liver and may come in contact with the anterior abdominal wall. The body (corpus) runs backward and upward and joins the neck of the gall bladder. That portion of the body which narrows as it approaches the neck is called the infundibulum. The neck of the gall bladder is short and angulated and leads into the cystic duct which connects the gall bladder with the common duct. The lining of the first half of the cystic duct (pars valvularis) is thrown into folds which have a spiral arrangement resembling a corkscrew and which are called the valves of Heister. The lower half of the cystic duct (pars glabra) has no valves.

The gall bladder is usually covered with peritoneum except on its upper aspect where it is united to the fossa of the liver in which it lies by thin loose areolar tissue. The remainder of the extrahepatic duct system consists of the hepatic ducts, right and left, which unite to form the common duct (choledochus). The common duct enters the second portion of the duodenum through an orifice in a nipplelike projection, the duodenal papilla.

Structure of the Extrahepatic System

Gall Bladder.—Microscopically the gall bladder consists of a mucosa, a fibromuscular coat, a subserous coat and the serosa. The mucosa is

Small fingerlike projections of the mucous membrane may be noted protruding toward and into the external muscle layers These are called Rokitansky Aschoff sinuses and are not true glands

The muscular coat of the gall bladder was discovered by Duverney[4] in 1701 and later studied in more detail by Heister[5] in 1717 and Hendrickson[6] in 1898 More recent studies include those of Lutkens[3] and Nuboer[7] In the body of the gall bladder the muscular coat measures from 0 075 to 0 1 cm in the distended state and from 0 2 to 0 5 cm in the contracted state Wide individual variations occur however Hendrickson states that there are no definite layers of muscle in the gall bladder but according to Lutkens and Nuboer it consists of two to five layers of flat broad plates of smooth muscle fibers arranged transversely longitudinally or circularly and mixed with fibrous and elastic tissue In the neck of the gall bladder a single layer of muscle with predominantly circular bundles is found The question as to whether a true sphincter exists at the neck of the gall bladder is still a point of discussion Some physiologic observations support the existence of such a sphincter while during fluoroscopy annular contraction rings in the region of the neck without evacuation of the gall bladder have been noted (Bronner[8] Kalk and Schondube[9] Kerley *et al*[10] Sandblom[11])

The sub erous coat is composed almost entirely of interlacing elastic tissue fibrils Occasionally one sees ductlike structures in this coat especially near the fundus or neck These are ducts of Luschka and may communicate with the bile ducts but not with the lumen of the gall bladder (Halpert[1]) The serosa is the reflection of the hepatic peritoneum on the gall bladder

Cystic Duct

The cystic duct has a mucosa submucosa and muscular layer The mucous membrane is composed of a single layer of columnar epithelium and a tunica propria which contains mucous glands and some muscle fibers The submucous coat is composed entirely of connective tissue The muscular layer varies depending on the portion of cystic duct examined The valvular portion is richer in muscular tis ue than the glabrous portion where there is mainly fibro-elastic tissue with few muscle fibers In the valvular portions the muscle fibers are predominantly in circular bundles Internal projections from these circular fibers (toward the inside) form the Heisterian valves (Macalister[13] Hendrickson[6]) It is assumed by Nuboer that the muscles in the valves of Heister help regulate the resistance to the flow of bile in both directions by contraction or relaxation

Hepatic Ducts and Common Duct

The mucosa of the hepatic ducts and common duct is formed by a single layer of epithelium with cryptlike depressions from which mucus is secreted These crypts are of importance in chronic bacterial infections of the common duct (See p 139) The muscular coat of the hepatic ducts and common duct above the sphincter of Oddi is mainly fibro-elastic tissue with few muscle fibers

thrown into tufts or folds covered by a single layer of columnar epithelium. The epithelial cells secrete mucus and at times deposits of lipoid material may be noted in the cytoplasm. Boyd[2] has studied these deposits extensively and has stated that the dried mucosa of the normal gall bladder contains from 0.51 to 1.70 per cent of cholesterol. In one case of strawberry gall bladder the percentage of cholesterol was as high as 60.54. According to Lutkens[3] mucous glands are present in the infundibulum and neck of the gall bladder as well as in the cystic, hepatic and common ducts.

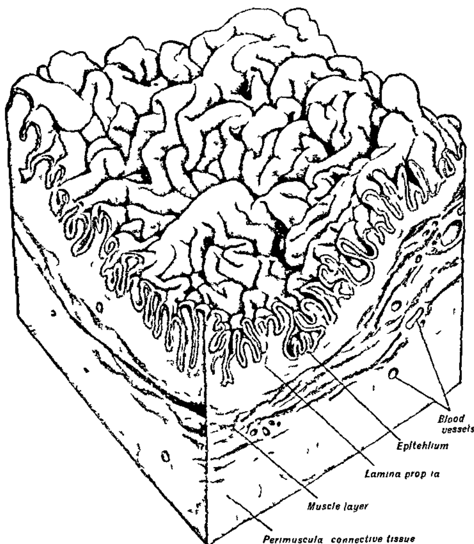


Fig. 3.—Camera lucida drawing of a block from human gall bladder. Stained with hematoxylin. 32 ×. (Drawn by Mr. E. Bohlman in Maximow and Bloom, Textbook of Histology, courtesy of W. B. Saunders Company.)

Small fingerlike projections of the mucous membrane may be noted protruding toward and into the external muscle layers. These are called Rokitansky-Aschoff sinuses and are not true glands.

The muscular coat of the gall bladder was discovered by Duverney[4] in 1701 and later studied in more detail by Heister[5] in 1717 and Hendrickson[6] in 1898. More recent studies include those of Lutkens[3] and Nuboer.[7] In the body of the gall bladder the muscular coat measures from 0.075 to 0.1 cm. in the distended state and from 0.2 to 0.5 cm. in the contracted state. Wide individual variations occur, however. Hendrickson states that there are no definite layers of muscle in the gall bladder, but according to Lutkens and Nuboer it consists of two to five layers of flat, broad plates of smooth muscle fibers arranged transversely, longitudinally, or circularly and mixed with fibrous and elastic tissue. In the neck of the gall bladder a single layer of muscle with predominantly circular bundles is found. The question as to whether a true sphincter exists at the neck of the gall bladder is still a point of discussion. Some physiologic observations support the existence of such a sphincter, while during fluoroscopy annular contraction rings in the region of the neck without evacuation of the gall bladder have been noted (Bronner,[8] Kalk and Schondube,[9] Kerley *et al*,[10] Sandblom[11]).

The subserous coat is composed almost entirely of interlacing elastic tissue fibrils. Occasionally one sees ductlike structures in this coat, especially near the fundus or neck. These are ducts of Luschka and may communicate with the bile ducts but not with the lumen of the gall bladder (Halpert[12]). The serosa is the reflection of the hepatic peritoneum on the gall bladder.

Cystic Duct

The cystic duct has a mucosa, submucosa and muscular layer. The mucous membrane is composed of a single layer of columnar epithelium and a tunica propria which contains mucous glands and some muscle fibers. The submucous coat is composed entirely of connective tissue. The muscular layer varies depending on the portion of cystic duct examined. The valvular portion is richer in muscular tissue than the glabrous portion, where there is mainly fibro-elastic tissue with few muscle fibers. In the valvular portions the muscle fibers are predominantly in circular bundles. Internal projections from these circular fibers (toward the inside) form the Heisterian valves (Macalister,[13] Hendrickson[6]). It is assumed by Nuboer that the muscles in the valves of Heister help regulate the resistance to the flow of bile in both directions by contraction or relaxation.

Hepatic Ducts and Common Duct

The mucosa of the hepatic ducts and common duct is formed by a single layer of epithelium with cryptlike depressions from which mucus is secreted. These crypts are of importance in chronic bacterial infections of the common duct. (See p. 139.) The muscular coat of the hepatic ducts and common duct above the sphincter of Oddi is mainly fibro-elastic tissue with few muscle fibers.

Asthmatic and emphysematic patients are however characterised by a very strong electrical activity during both parts of the respiratory circle Occasionaly it may be seen that interruption of an acute attack by a bronchospasmolytic agent is followed by a prompt decrease or cessation of the spasm

It is our opinion that the spastic activity of the diaphragma and of the other inspiratory muscles is induced by stretch receptores in the bronchial wall which are connected by vagal fibres to the respiratory center Time is too short to explain this probable mechanism.

It may be therefore that Biermer was as right as Winthrich both the bron chiolar spasm and the cramp of the inspiratory muscles taking part in the pathog nesis of the asthmatic dyspnoea

FURTHER OBSERVATIONS ON THE EFFECT OF SPECIFIC HYPOSENSITIZATION IN ASTHMA *

by

EGON BRUUN

Bray once said 'The capriciousness of asthma is one of the most fascinating even at the same time disturbing factors in the study of the subject Probably most of you will agree that also the *diagnostic problems* in asthma are both fascinating and worrying questions and I feel convinced that you all share my feelings about the *treatment* of asthma which is at the same time a fascinating and wonderful inspiration and on the other hand so capricious a task that it may bring you to the point of a nervous depression

When in a capricious disease one is working with both capricious diagnostic procedures and capricious forms of therapy the evaluation of the therapeutical results must be a somewhat delicate affair To day the Committee has wanted an evaluation of one of the various forms of treatment of asthma the specific hyposensitization but it must be stressed at once that specific hyposensitization is not the only form for treatment of asthma and in some cases not even the best one However on the basis of more than 14 years experience I daresay that a specific hyposensitization based on a sound and critical diagnosis in most cases of asthma offers the patients a better future than other forms of treatment

When in 1941 the Allergy Clinic in Copenhagen was opened the following three questions had to be taken into account

1) How often is asthma an allergic disease?
2) How often will it be possible to demonstrate the etiological causes?
3) Will specific hyposensitization be effective?

The literature did not help us much In the hands of reliable scientists the results of specific hyposensitization in asthma varied within very wide limits improvement being stated in from 20 to 90 per cent

Therefore we set ourselves the task to apply such diagnostic procedures that a reliable allergy diagnosis was obtained and to procure a material of patients which would clearly demonstrate the value of specific hyposensitization

* From the Medical Outpatients Department University of Copenhagen Subdivision for Allergic Diseases (Egon Bruun M.D)

Already in the twenties the early Dutch allergy school (Storm van Leeuwen Tissot van Patot and Varekamp) advocated exogen allergens as the main cause of asthma and on the basis of the anamnesis cutaneous diagnostics provocation tests elimination procedures and several other

TABLE 1

Results of specific hyposensitization in 239 asthmatics period of observation 6—12 months (Bruun 1945)

	Number of patients	%	Average duration of asthma
Without symptoms	50	20 9 % } = 88 2 %	7 0 years
Improved	161	67 3 %	9 1 years
Unchanged	27	11 2 %	11 6 years
Worse	1	0 5 %	
Total	239 patients		

examinations we arrived at the conviction that in most cases (probably all) asthma is an allergic condition and that in most cases an adequate exogen allergen can be demonstrated as the etiological cause

On purpose it was decided to treat all cases of asthma whether complicated or not in which an allergic condition was considered the basic factor with specific hyposensitization and to use this treatment as the only form of adequate therapy The programme was divided in various stages First 239 patients were treated with one single series of hyposensitization lasting 2—3 months The results will be seen from table 1 (period of observation 6—12 months)

Secondly the same patients and several additional cases (a total of 478) were reexamined after a period of observation of about three years and some of the patients were treated with more than one series of injections As might be expected the good immediate results were not lasting and after a lapse of three years the percentage of improvement dropped from 88 to 60 (Table 2) and finally it could be doubted whether specific hyposensitization is in reality superior to other forms of asthma therapy because in a control material Henriksen found a percentage of improvement of 52 It seemed however as if the results were improved if the patients were treated with repeated series of hyposensitization (Table 3) which may indicate that by a continous treatment over a period of several years the results might be improved

Before this however the influence of the psychological factor in asthma-therapy had to be evaluated To this purpose placebo examinations were carried out For a period of 18 months house dust allergic asthmatics with odd case record numbers were treated with the specific

TABLE 2

Results of specific hyposensitization in 478 asthmatics period of observation 3 years (E Henriksen 1951)

	Number of patients	%	
Without symptoms	36	7 5 %	} = 59 8 %
Almost without symptoms	38	7 9 %	
Improved	212	44 4 %	
Unchanged	108	22 6 %	
Worse	51	10 6 %	
Dead	33	6 9 %	
Total	478 patients		

TABLE 3

Results of specific hyposensitization in relation to the number of series of injections (E Henriksen 1951)

Number of series of injections	Number of patients improved	%
1	146	57 2 %
2	69	57 0 %
3	38	65 5 %
4	21	75 0 %
5 or more	12	75 0 %

extract and house dust allergic asthmatics with even case record numbers were treated with placebo from table 4 it becomes evident that specific treatment is superior to treatment with placebo Erik Andersson is his studies on the effect of cortisone and ACTH therapy in asthma also made placebo experiments and arrived at the same figure 4 out of 11 patients i e about one third improved with placebo treatment

These investigations demonstrate that when the patients are given the impression of being under adequate and proper treatment one third

will state improvement independent of what kind of treatment they have been submitted to This must be borne in mind whenever a new form of therapy claims to give results in asthma

In 28 patients we were able to carry out a kind of double control as these 28 were first treated with placebo and then after a suitable period of observation—with the specific allergen From table 5 it appears that

TABLE 4

Control examinations of the specificity of specific hyposensitization (Bruun 1949)

	Specific hyposensitization		Placebo treatment		Total
Without symptoms	13 6 %	78±4 3 %	3 7 %	34±5 3 %	
Improved	64 2 %		30 5 %		
Unchanged	18 9 %	22±4 3 %	54 9 %	66±5 3	
Worse	3 2 %		11 0 %		
Number of patients	95		89		184

TABLE 5

28 house dust allergic asthmatics first treated with placebo injections subsequently with extracts of housedust Probable mean error on the mean figures 7.9 % and 8.3 % (Bruun 1949)

	Placebo treatment		Specific hyposensitization	
Without symptoms	0	21 %	2	75 %
Improved	6		19	
Unchanged	19	79 %	5	25 %
Worse	3		2	

that 22 out of 28 patients remained uninfluenced by placebo treatment whereas in the same group of patients only 7 out of 28 did not improve after specific hyposensitization

On the basis of Dr Henriksen s observations that the results are improved by repeated series of injections we started in 1951, a con tinous form of specific hyposensitization in the way that a continuation course of the strongest dose—generally 0 7 ml of a 1 100 dilution—is given once every second or every third week for three years After

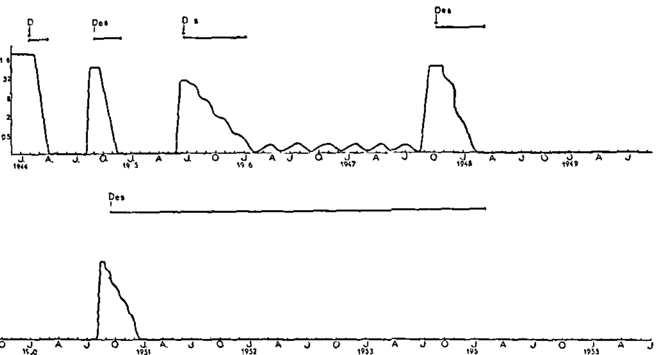
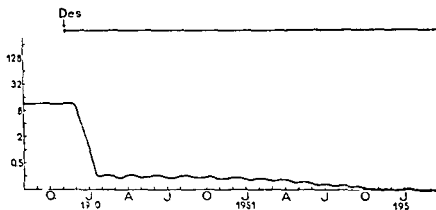


Fig 1

662/44 ♀*1890 Asthma since 1933 house dust allergy
Ordinate average duration of asthma attacks (hours/month)
Des = Specific hyposensitization
See page 29



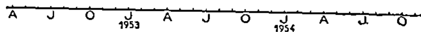
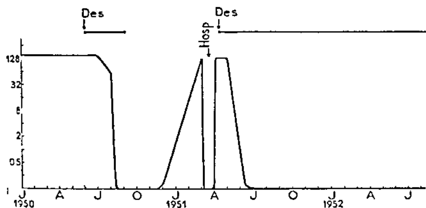


Fig 2

3248/49 ♂ 1911 Asthma since 1949 Allergy to feathers and house dust



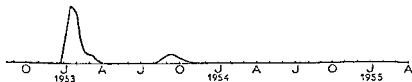
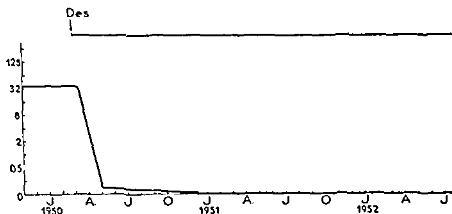


Fig 3

1798/50 ♀ 1913 Asthma since 1947 Allergy to house dust and feathers (and salicylates)



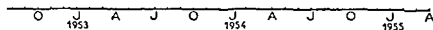


Fig 4

40.2/49 ♂ 19 0 Asthma since 1930 Allergy to feathers and house dust

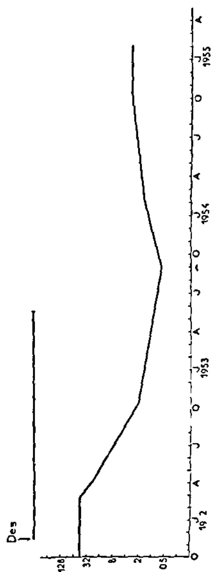


Fig 5

3 60/45 ♂ *1925 Asthma since 1943 flour (baker)

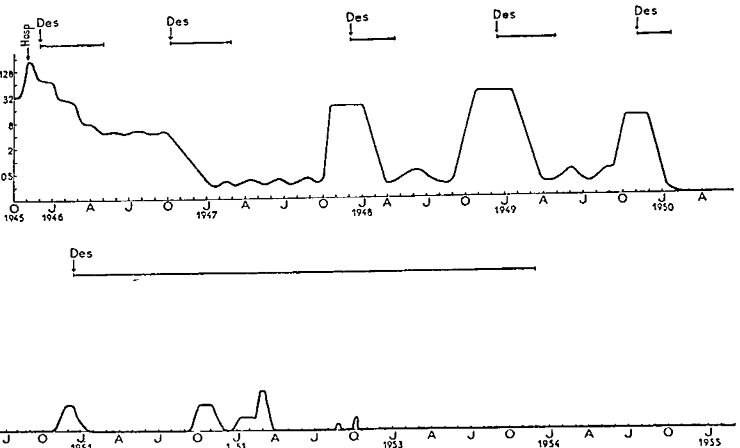


Fig 6

2269/45 ♂ 1907 Asthma since 1944 house dust allergy

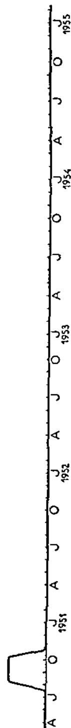
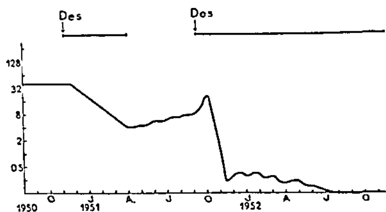


Fig 7

640/45 ♂ **1908 Asthma since 1974 house dust allergy*



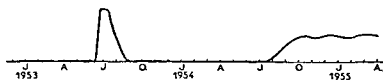
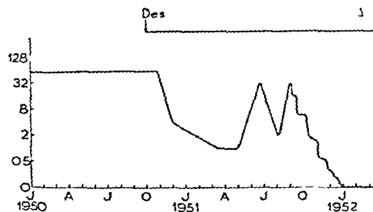


Fig 8

3852/50 ♀ 1883 Asthma since 1919 Allergy to house dust and feathers



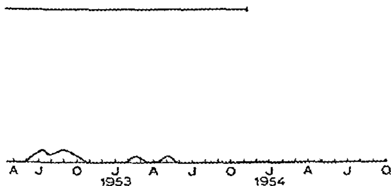


Fig 9

3412/50 ♂ 1904 Asthma since 1949 house dust allergy

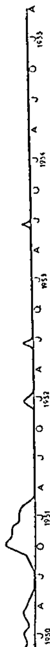


Fig 10

572/44 ♂ 1901 Asthma since 19 6 house dust allergy

three years treatment the injections are discontinued and the patients are kept under observation for a period of another three years As mentioned above this experiment was started in 1951 and consequently has not been finished yet but on this occasion some preliminary results can be discussed The definite evaluation must be postponed for another two years or maybe even more A total of about 5—600 patients *are included in the experiment To elucidate the asthmatic condition in* each patient I have tried to make a graphic illustration a diagram for each patient In a co ordinate system the average duration of asthma attacks per month forms the ordinate and the time of observation constitutes the abscissus When for instance a patient claims to have asthma for about one hour every night the duration of his attacks is estimated at 30 hours per month In another case the patient may state that he suffers from asthma constantly for 2—3 days in connection with colds and that he gets such colds every second month in this case too the monthly duration of asthma will be estimated at about 30 hours From these examples it appears that the diagrams cannot give information about the type of asthma but it can give you a rough idea of the effect of a long term treatment On pages 19—28 such ten diagrams are reproduced These ten have not been subject to any selection they simply represent the ten first of the series Better examples could be demonstrated if they were picked out of the material but it seems more suitable for the purpose to show you these cases that have not been selected

From diagram 1 it will be seen that a patient with a severe bronchial asthma of a duration of 11 years can be regulated by specific hyposensitization It will be seen too that the first attempts of hyposensitization (in February—April 1944 in September—December 1944 in June—December 1945 in August 1947—February 1948) resulted in relatively short periods of relief but sooner or later she had relapses When in September 1950 the continous form of hyposensitization was commenced she obtained a permanent freedom of asthma which has till now lasted for more than a year *after* discontinuance of the treatment

There is nor eason to go into details with the rest of the diagrams as all necessary information can be obtained from the tables but it must be mentioned that in one case diagram 5 the therapeutical result was unsatisfactory In this case the curve never reached the bottom line i e the patient never got free of symptoms The patient is a baker with allergy to flour and it seems reasonable to consider the daily exposure to the specific allergen to be too intense a factor to obtain a good result with hyposensitization

As to the intradermal reactions it could be stated that after three

years of treatment they were definitely weaker than before treatment On the other hand the vital capacity did not seem to be influenced by hyposensitization

TABLE 6

Mortality rate in asthmatics treated with specific hyposensitization and in asthmatics otherwise treated

	Specific hyposensitization	Control material
Malmros & Rydberg 1944	1 per cent	4 per cent
E Henriksen 1951	2 9 per cent	4 9 per cent

TABLE 7

Rate of invalid pension granted in specifically treated asthmatics and in asthmatics otherwise treated (E Henriksen 1951)

Specific hyposensitization	1 9 per cent
Control material	6 1 per cent

Besides the direct effect on the asthmatic conditions some other factors must be dealt with when you want to evaluate the benefits of specific hyposensitization It is generally agreed that about 5 per cent of asth matic patients die from asthma Of the many statistics one of the latest will be quoted McCracken from Dr Williams Clinic at Cardiff in a follow up of 80 asthmatics over a period of 10—12 years found 10 per cent died 5 per cent from asthma Already in 1944 Malmros & Rydberg of Sweden demonstrated a smaller mortality in specifically treated asthmatics than in controls Henriksen made the same observation (table 6)

In addition Henriksen found a remarkable difference in the number of asthmatics who got an invalide pension in the control group (6 1 per cent) and in the group of specifically treated patients (1 9 per cent) see table 7

Finally the value of the specific allergic diagnosis without other treatment besides that of elimination should not be overlooked but is not within the scope of to day s subject

On the basis of these observations we feel it justified to recommend specific hyposensitization in asthma as a long term treatment Whether three years of therapy is necessary cannot be decided yet probably a more individual treatment should be aimed at on the basis of the strength of the intradermal reactions On the basis of our experience it seems reasonable to continue the hyposensitization until the cutaneous reactions become definitely weaker than before treatment Although there are exceptions the general rule *is* a correlation between good results and definitely weakened intradermal reactions

The effect of the specific therapy stands and falls with the right etiological diagnosis It is not sufficient to demonstrate a positive cutaneous reaction several other factors must be taken into account when the allergic diagnosis is established

Failures in specific hyposensitization are due to a wrong diagnosis —false reactions unspecific reactions etc —or due to a neglect of a specific cause which should be removed from the patient s environment

At last it must be emphasized that specific treatment cannot cure the *complications* of asthma neither bronchitis emphysema bronchiectasis nor sinusitis Too often the allergist is blamed because of poor results in conditions that have nothing to do with allergy Therefore we must try to get the patients to commence treatment as early as possible before chronic complications have developed

References

ANDERSSON F *Ambulant behandling af asthma bronchiale med ACTH cortison og hydrocortison* Thesis Munksgaard Copenhagen 1954
BRAY GEORGE W *R cent Ad ances in Allergy* Churchill Ltd London 1937
BRUUN E *Nordisk Med* 28 2581 1945
— *Acta All rgol* 2 122 1949
HENRIKSEN E *Asthma b onchiale* Thesis Dansk Videnskabs Forlag Copenhagen 1951
MALMROS H RYDBERG G *No disk Med* 21 539 1944
MCCRACKEN D *B it Med J* I 409 1950
STORM VAN LEEUWEN W *Allergische Krankheiten* J Springer Berlin 1928
TISSOT VAN PATOT P N *Het uits hak len van de exogene oor‚aken van het kl maat-asthma als the apeutische maat eg l* Thesis Leiden 19 9
VAREKAMP H *De exogene oo zaken van asthma bronch ale* Thesis Le den 19‚5

FAILURE OF SPECIFIC DESENSITIZATION IN THE TREATMENT OF BRONCHIAL ASTHMA

by

P J VAN DER WERFF

The causal aetiological treatment of bronchial asthma should be based on

a) Systematic examinations made to detect the determinants which differ markedly in each individual case allergic factors endocrine disturbances focal infections etc

b) if possible the elimination of these factors

c) and as regards the allergic factors especially air borne allergens hypo- or desensitization (as avoidance of the inhalants is not always possible for practical and/or social reasons

Valuable though it may be this method does not always yield beneficial results[3, 1]

These failures are due to various causes

1) *The incorrect selection of allergens* owing to inaccurate or incomplete investigations and tests for air borne substances and foods which might be a possible cause of allergy in the patient concerned will a priori result in the failure of specific desensitization

As regards the house dust problem it may be stated that preparation of an extract from dust obtained from the house of the patient combined with examination of the dust samples for the presence of fungi is essential in cases in which skin tests for allergy with standard house dust extracts are negative and the history of the patient suggests hypersensitiveness to dust Utterly unexpected and unusual associations of fungi were observed in some exceptional cases (f i Aleurisma Guilliermondi Grigoraki Absidia ramosa (Lindt) Lendner Botryosporium *longibrachiatum Oud* or *Thielariopsis paradoxa (de Seynes) v* Hohn Acrospeira levis Wiltsh) We use the fine dust gathered from mantelpieces furniture etc, in preparing house dust extracts rather than the coarse dust collected by the vacuumcleaner Among other things the latter often contains animal hairs and coarse particles of street refuse substances apt to cause a marked non specific secondary reaction which may lead us into error in evaluating the results of skin tests for allergy both those of the first skin test and those of the subsequent tests during desensitization

The *chief factors* which have to be especially taken into account in the Netherlands—if we wish to avoid omissions in examining patients

for allergens are house dust moulds pollens old kapok bed feathers sea weed waste wool oat husks dried ferns and Alp grass for stuffing mattresses pillows and upholstered furniture mites haystack and cornstack dust animal dander foods We found no demonstrable allergy in about 6 per cent of the cases

As regards occupations and trades it may be stated in general that the most frequent and severe cases of asthma may be anticipated wherever vegetable or animal substances are used in industry and the micro flora of spoilage fungi with fairly constant associations specific of each of these substances is present [3]

2) *Incorrect indications* will inevitably result in disappointments We shall briefly review some of the principal clinical pictures

a) Detailed examination of the sputum and x raying are essential in establishing a differential diagnosis in patients with asthma showing symptoms of bronchitis [19]

Specific desensitization may be naturally be expected to be succesful in *eosinophilic non bacterial bronchitis* as it actually is a chronic asthma of allergic origin marked by the production of a viscid mucous occa sionally foamy sputum which always contains a large number of eosinophils whether or not accompanied by acute attacks of asthma

Failures are bound to occur when by an unsufficiently detailed examination specific fungus desensitization cure is administered *in cases of bronchial asthma secondary to mycosis or thrush of the bronchi and lungs* [2] [31] The internal source of allergens should be destroyed by medical or surgical treatment in these cases irrespective of whether an active inflammation is involved or a silent growth of fungi has occurred in the respiratory tract

There is a chance of failure when the wrong time has been chosen to start desensitization viz *in cases of chronic asthmatic condition with secondary infections by bacteria* These cases usually show inflammations caused by Haemophilus influenzae pneumococci Staphylococcus aureus Neisseriae or combinations of these bacteria [2]

With a few exceptions the asthma was either seen to remain un changed or even to show frequent signs of aggravation in these patients when antibiotics were administered *prior to* anti allergic treatment [20] [15] The cause of this phenomenon continues to be obscure

Specific desensitization has no effect on possible *bronchiectasis* asso ciated with asthma a frequent complication

b) Once a *substantial emphysema* has developed possibly accompanied by cor pulmonale desensitization will not result in its disappearance This treatment will only be of use when the condition is associated with attacks of allergic asthma In our experience there is a considerable chance of general systemic reactions in these cases we don t know why'

All this implies that complications should be prevented if possible by early anti allergic treatment preferably as early as the stage of vaso motor rhinitis which so often precedes bronchial asthma

3) *The incorrect use and/or too short a duration of specific desensiti zation* is conducive to failures

The usual method viz the subcutaneous injection of increasing doses whether or not under the protection of adrenaline sympatol anti histaminics ACTH prolongatum and cortisone may rapidly induce a state of hyposensitiveness in various cases of asthma with rush desen sitizing therapy [9] This treatment is especially useful in preventing relapses following the return of the patient to his home surroundings after hospitalization No satisfactory results will be obtained however unless treatment with 2—3 weekly injections is continued for at least six months another eighteen months during which maintenance doses are given at increasingly long intervals being required to obtain results positive both from the serological and clinical point of view

This is especially true of patients allergic to seasonal moulds and individuals engaged in particular trades and occupations such as far ming the baking trade flour mills or the textile wood and leather industries

In our experience this only applies to air borne allergens

For we have never observed tangible results obtained by subcutaneous injections against foods

Occasional treatment with skeptophylaxis or prolonged habituation or desensitizing by oral administration of gradually increasing doses [23, 27, 13] did indeed result in some improvement in scarcely 17 per cent of a group of 260 patients with characteristic food allergy in our hospital On the other hand psychogenic factors played such an important role in the not so many cases in which treatment was completely succesful that even the results obtained in these subjects do not accurately reflect the true state of things Therefore Willem Kremer who devoted particular attention to the problems of food allergy for many years believed these methods to be of little use in treatment

Our own experience has not been sufficient to give an opinion re garding the value of spray inhalants [17] and oral methods in the treat ment of inhalance allergy [9, 2, 23] and Urbach s oral propeptane the rapy [30] the sublingual [10] the intracutaneous [24] and the intramuscular methods of administration of allergenic extracts prepared from inhalants and foods

Confining ourselves to desensitization against inhalants the next cause of failure may be stated to consist in

4) *errors of dosage* Too small doses may occur as all liquid allergenic extracts decrease in allergenic potency slowly in some cases rapidly

in others among other things this depends upon the temperature at which the vaccine is stored and the type of fluid used in preparing extracts Recently prepared liquid pollen and fungus allergenic extracts sometimes show a particularly rapid decrease even in the first days Clinically this involves the danger that the first injections of such a recently prepared vaccine might give rise to general systemic reactions (When desensitization was administered in low dosage during a rather long period this treatment sometimes has yielded excellent results)

Apart from the danger of systemic reactions [5] in our experience a failure is most liable to occur when *too large doses* of the extracts pre pared from pollens moulds and yeasts are administered (cf p 40)

When patients are being tested or treated with drugs regardless of the method of administration danger is present [7] Special mention should be made of this *drug allergy* which sometimes e g when using pulv *rad ipecac and pulv fol digitalis does but frequently does not induce* a local wheal in skin tests for allergy [11] Severe systemic reactions may occur unexpectedly in these cases as we saw in skin tests with aspirin and diphantoin and also observed in the case of a worker employed at a pharmaceutical factory who was hypersensitive to neo arsphen amine

5) Likewise *an incorrect evaluation of the results of skin tests for allergy during desensitization* may provide unpleasant surprises One should be careful in evaluating the reliability of local wheals as a sole test of the stage of hyposensitiveness or desensitization respectivily Like others [6b] we frequently observed that an initial increase of the local reaction in the early stage of treatment was followed by a decrease accompanied by a progressive improvement of the clinical symptoms of allergy Undoubtedly this was not true in all cases In that event the skin reactions continued unchanged or disappeared entirely regardless of the result of treatment [16 4 18 1]

Thus some cases showed an improvement without skin tests differing significantly from the initial reactions whereas the positive skin reactions even decreased or disappeared in others which had to be defined as failures from the clinical point of view The statement that one should be careful in increasing the dosage in the case of a markedly strong skin reaction continues to apply in clinical cases One should be double careful in the event of none only a slight or a delayed reaction

It is virtually impossible in practice to determine the quantity of circulating serum reagins and possibly that of blocking antibodies at regular intervals In addition the latter are not always produced not even when large doses can be tolerated This is true e g in the case of house dust and in that of the lignase and cytase producing fungus Trichoderma viride Pers ex Fr as I was able to observe personally

When the variations in the results of the skin tests for allergy made to verify the effect of treatment during desensitization are studied in the light of current serological knowledge they will after all be understandable to a considerable extent

Without wishing to minimize the work of other investigators in this field attention may be drawn to certain milestones the introduction of specific desensitization in human medicine (Freeman Noon 1911) the demonstration for the first time of inhibitors in the blood of asthmatic patients with fungus feather and cat s hair allergy (Storm van Leeuwen and Kremer 1927 Kremer 1932) the rediscovery of these inhibitors in the blood of patients with hay fever (Cooke c s 1935) the determination of the nature and point of action of antibodies inhibiting the reaction (Van Dishoeck c s 1942)

In the opinion of Van Dishoeck —and we are in complete agreement with this view— the decrease of the sessile tissue reagins and an increase of circulating reagins (state of hyposensitiveness) is followed by the actual desensitization caused by the blocking antibodies which as he showed act upon the reagins and which he therefore called *antireagins* [6a, 6b]

It is conceivable that in some cases of failure there may be a likelihood of a compensation situation occurring in an occasionally permanent intermediate stage between the increase in reagins and the production of antireagins including the possibility of other so far unidentified factors

6) Accordingly excluding other causal determinants there are a number of *patients who are unable to acquire a state of hyposensitiveness or desensitization* In these cases there was a certain tolerance to the allergens This was shown even by adequate large dosage of allergens subcutaneously administered although the air borne allergens were not tolerated in the exposure and inhalation provocative tests and likewise no definite improvement subjectivally and clinically resulted

7) Moreover there are patients who by causes hitherto unknown have *an intolerance to the allergens involved* even when treated with extremely small doses and with protective drugs

Despite all our precautions taken in asthmatic patients with inhalance allergy symptoms persist in at least one third of the total number of patients approximately the same number as in vasomotor rhinitis

No one will doubt the value of specific desensitization Anaphylactic animal experiments have provided conclusive evidence of its use Failures hardly ever occur in animal experiments although individual and generic quantitative variations may be observed

There are much more doubtful factors in men however so that the risk of a large number of failures must be taken into account

The realization and study of these failures are of particular importance as they may possibly put us on the track of the other causal factors which in addition to sensitization play a role in bronchial asthma

SUMMARY

The causes of failure in treatment of bronchial asthma by specific desensitization are reviewed

Failures may be due to

- the incorrect choice of allergens
- incorrect indications
- use of an incorrect method of specific desensitization
- incorrect evaluation of the results of skin tests for allergy
- inability of the patient to acquire a state of hyposensitiveness or desensitization
- intolerance to the allergens involved

References

1 Baldwin L B Glazer I J *Alle gy 8* 129 1937
2 Black J H *J Lab and Cl n Med 12* 1156 1927 *13* 709 19_8
— *J Allergy 10* 156 1938
3 Bruun E *Nord Med 28* 2581 1945
— *Acta Allergol 2* 122 1949 *Suppl I* 239 1950
4 Colmes J *J Alle gy 3* 449 193 *4* 98 1933 with discuss on
— et al *J Allergy 4* 473 1933
5 Cooke R A *J Immun 7* 119 192_
6 — et al *J Exp Med 62* 733 1935
6a Dishoeck H A E van Klein S P *Ned Tydschr v Geneesk 86* 2699 1942
— — *Acta M d Scand 115* 331 1943
6b Klein S P Thesis Amsterdam 194
7 Flaxman N *J A M A 147* 377 1951
8 Freeman J *J La cet I* 630 1911 *II* 814 1911
9 — *J Lancet I* 744 1930
10 Hansel F K *Cl nical Alle gy* p 528—530 St Louis 1953
11 Hansen Pruss O *Ann Allergy 7* 217 1949
12 Henriksen E *Acta Alle gol I* 204 1948 *6* 208 1953
13 Keston B M et al *J Allergy 6* 531 1935
14 Kremer W *Zeits hrift f Imm n Forsch 78* 382 1933
15 — v d Werff P J *Aanw D agn The ap Geb* VII p 416 1952
16 Lamson R W et al *Am J M Sc 175* 791 1928
17 Mackenzie G M (Baldwin L B) *A ch I t Med 38* 7 2 1921
— — *J A M A 78* 787 1922
18 Markow H Spain W C *J Alle gy 4* 363 1933 *6* 227 1935
19 Mulder J Thesis Groningen 1937 *Ned Tydschr v Gen 9* 3521 1948
— *Aanw D agn Therap G b* VII p 4—15 195?
20 — *Aanw D agn The ap G b* VII p 25 1952
21 Noon L *J Lancet 1* 1572 1911
2_ Orie N G M Thesis Groningen 1946

23 PASTEUR VALLÉRY RADOT et al *Presse méd* ?9 764 19 8
24 PHILLIPS E. W *J.A.M.A* *86* 182 19.6
25 PLAS M C VAN DER Thesis Leyden 1951
26 STORM VAN LEEUWEN W KREMER W *Zeitschr f Immun Forsch* *50* 462 19?7
27 ROWE A H *J Allergy* *3* 69 1931
?8 THOMMEN A. A in COCA A F WALZER, M THOMMEN A A, *Asthma Hayfever Theory and Practice* Springfield 1931
29 TOUART M D *New York M.J* *116* 199 19 ?
30 URBACH L *Ann Allergy* *1* 219 1943 *3* .87 1945 *5* 147 1947 *5* 225 1947
31 WERFF P J VAN DER *Ann Allergy* *11* 567 1953
32 WESTERDIJK, JOH.A *Antonie v Leeuwenhoek* *15* 187 1949

DISCUSSION

SOME PROBLEMS CONCERNING THE RESULTS OF TREATMENT WITH SPECIFIC HYPOSENSITIZATION

by

HELGE COLLDAHL

Three factors are of special importance in the treatment of asthma apart from the attacks They are specific hypersensitivity bronchial infection and focal infectious processes

It is very important to stress when judging the result of asthmatic treatment that the asthmatic troubles in a special case are often caused by multiple factors and that the result of the treatment depends upon how important factors could be more or less eliminated by the treatment

The effect of specific hyposensitization must therefore be dependent upon the degree of importance of the specific cause of the asthmatic troubles in the special case Regarding different asthmatic patients for whom specific causes are of importance the specific factor is of extremely varying significance for the devel opment of the asthma Therefore specific hyposensitization must differ greatly in importance in different cases even if specific hyposensitization is only given when specific allergic factors are of importance for the asthmatic troubles I therefore think it is of extreme value to investigate by the help of provocation tests and so on as to how important the specific cause is in a special case

In a series of 387 asthmatic patients investigated 1950–1953 at the allergy laboratory of the m dical clinic of the University of Lund Sweden there was indication for specific hyposensitization in about 25 per cent (Lund is a small town most of the patients come from the country around)

Of the 387 patients 229 (59 per cent) showed a positive skin test while 158 (41 per cent) showed a negative 43 per cent of the patients with positive skin test gave a positive provocation test The best indication for giving specific hyposensitization in our opinion is a positive provocation test

The patients to whom specific treatment was given have also received other forms of therapy Of these patients I have had the possibility to follow 53 for ½—3 years The specific treatment was continued during a long time 2—3 years 47 per cent had no troubles or were very much improved 19 per cent much improved 19 per cent improved In 4 per cent no improvement occurred In 5 5 per cent it was impossible to carry out the treatment and in 5 5 per cent the patients declined to complete the treatment

Thus a result of the combined *therapy was obtained in 85 per cent*

I think nobody can deny the effect of sp cific hyposensitization in a case where specific factors are of great importance The fact that in certain cases the result of specific hyposensitization is only slight must not necessarily be interpreted as failure of the treatment In such cases the effect of the specific factor can have been completely eliminated but the importance of the specific factor was only

slight and other factors were of much greater importance Combined treatment is often necessary For the successful treatment of asthma it is important that as many different etiologic factors as possible are detected and eliminated or treated Of special importance it must be to treat or eliminate the most significant causes

Many authors have considered it important to have a control material when judging the results in cases where specific treatment had been given Some of these authors have as control material used cases where a specific sensitivity had not been detected Under such circumstances the control material according to my opinion cannot easily be compared with the group where specific factors are of importance The groups are unlike If one wishes to have a control material it is necessary for such an investigation to choose cases as similar as possible in all respects and to treat only every second with specific treatment This was done by Bruun 1949 I think that a large investigation in that way would be of great importance

References

AARSWOLD C N *Nord Med 33* 239 1947

BRUUN E *Acta Allergol 2* 122 1949

COLLDAHL, H *Acta Allergol V* 133 1952 *V* 143 195? *V* 154 195_

— *Nord Med 5?* 966 1954

HENRIKSEN E *Asthma bronchiale* Dansk Videnskabs Forlag A/s Copenhagen 1951

MALMROS H RYDBERG B *Nord Med 21* 539 1944

SPECIFIC DESENSIBILIZATION

by

A W FRANKLAND

There are very many reasons why when desensitization has been decided upon the results are not as good as might be expected I should like to mention one aspect only and this is concerned with the dosage Quite often and possibly because of the fear of general reactions but also because of the large number of injections required *a sufficiently high dose is not reached in the course of* desensitization This was well shown in a recent controlled trial carried out in patients with seasonal hay fever (Frankland *Acta Allerg* 1956 in the press)

REPLY TO DR FRANKLAND

by

P J VAN DER WERFF

I wish to thank Dr Frankland for his supplementary comments Our experience has indeed also shown *that administration of too small doses* may ultimately result in hyposensitiveness In using this method however too much valuable time is wasted unnecessarily and practice has shown that in this event the patient (or the physician) sometimes becomes discouraged without need and too soon

When the *dosage is too large* the case is quite different

1) this involves the risk of a more or less severe general systemic reaction and
2) the organism may continue in the stage of hypersensitiveness as is also the case with all allergic patients who constantly or at regular intervals inhale asthmogenic quantities of allergens which also fail to induce a state of hyposensitiveness

It may possibly be worth mentioning that in the past years I treated three patients who had a shock due to administration of too large doses this immediately resulted in a state of hyposensitiveness in two of these patients the third had become intolerant however as was shown by administration of the weakest dilutions

Case 1 Miss C F aged 22 a seamstress hardly able to work as a result of severe bronchial asthma and vasomotor rhinitis and showing a marked hypersensitiveness to house dust of her own home as well as to certain species of Aspergillus (viz versicolor (Vuill) Tiraboschi ochraceus Wilhelm Amstelodami (Mang) Thom et Church nidulans Eidam) which along with Rhizopus nigricans Ehrenberg were found to be the fungi prevailing in her home (neither skin tests nor inhalation tests with standard house dust or other fungi had been positive) The responses in the positive skin tests were markedly strong the 4th injection given in the course of desensitization was seen to result in a local reaction measuring 2 by 3 cm and mild symptoms of vasomotor rhinitis The fifth injection resulted in a severe dyspnoea appearing within a few minutes and a state of shock which persisted for 3 hours Subsequent skin tests and inhalation tests were negative even when increasing doses were administered Since that time she has had no further attacks of asthma Follow up 5 years

Case 2 Mr W den H aged 41 an electrician affected with very severe asthma which had rendered him unfit for work for 6 months past The patient showed a marked hypersensitiveness to house dust and all dominant fungi in the home The first 5 injection given in the course of desensitization resulted in marked local reactions the fifth injection being also a sociated with a mild attack of colica mucosa the sixth injection however gave rise to a very severe shock The patient subsequently continued entirely free of symptoms for well over one year and six months The symptoms then gradually increased again an improvement being obtained by a prolonged course of desensitization in low dosage

Case 3 J H aged 17 employed at an old metal rag and waste paper store affected with severe progressive asthma and vasomotor rhinitis Markedly allergic (both serologically and clinically) to industrial dusts and fungi The first two injections gave only one + local wheal the third injection of the 1 per cent vaccine administered in increasing doses immediately resulted in vasomotor rhinitis which showed signs of increasing manifestations during the next days and was followed by dyspnoea on the sixth day After an interval of a fortnight during which the patient showed no symptoms injection of a 1 10 dilution of this vaccine resulted in continued attacks of severe dyspnoea persisting for 2 days Three injections of a placebo failed to elicit any response but administration of a 1 100 dilution was followed by shock marked by general distress severe

dyspnoea and a brief collapse A placebo was given for a few weeks followed by administration of a 1 100 000 dilution resulting in a marked local reaction mild dyspnoea in the evening and a mild degree of vasomotor rhinitis appearing the next day

I previously reported the case of a patient with hay fever who initially showed marked local reactions in view of which fact great caution was used in desensitization In the third year the local reactions had diminished and the doses were increased somewhat more rapidly which unexpectedly resulted in a very severe state of shock The first subsequent injections gave rise to local reactions which were as marked as they had been at the beginning of desensitization cure

SPECIFIC TREATMENT OF ASTHMA

by

R ALEMANY VALL

The treatment by pollen is quite efficient at the first stages of the pathologic condition these stages are counted by seasonal years when only conjunctivitis or rhinitis are present Later when asthma appears — also of pollinic origin — although the whole picture may disappear specially in those sensitive to gramineous plants in those who are sensitive to other pollens a more or less seasonally evident rhinitis may remain present in spite of specific treatment

In Barcelona we have patients sensitive to gramineous plants whose symptoms disappear even in the course of the same season if they are then subjected to the treatment but do not appear during the season if the pre seasonal treatment has been followed

Patients sensitive to Platanes (Plutanus orientalis) suffer from rhinitis and asthma improved by the treatment although generally not quite so much as is the case with those sensitive to gramineous plants this occurs also in those sensitive to Parietaria officinalis of which many cases may be seen on the Mediterranean Coast this depends on the larger diffusion of pollen in the local ambient air of the patient in proportion to neighbouring plants When there is a large quantity of pollen present the treatment may even give opposite effects

We administer injections on alternate days or one every week or two weeks per tenth parts of 100 – 10 000 units this specificity is the clearest and most evident of all allergic affections Cutaneous reactions remain positive even out of season — these reactions to certain pollens will recur even years afterward in patients without any crisis or very slightly affected (Parietaria)

Those sensitive to Chenopodium Album respond very well to the treatment We found this pollen not only at the beginning of autumn but also in summer spring and even in winter

We have not seen pollinic crises only appearing during the night we have seen however night-crises in patients suffering from daily crises we have seen hardly any pollen in the house of the patients and found little at night on the slides

We saw cases sensitive to the pollens of Cosmos Aster Gladiolas Daisies etc in florists showing large cutaneous reactions and even focal reactions by simple scarification with pollen above them We do not advise a desensitizing treatment for these patients living in contact with these plants and whose crises begin already in June

Those sensitive to both pollen and dust when the latter is widespread in the ambient air of the patient but only in months of intensive pollen formation specially in Parietaria (April – May or May – June) must be treated only with pollen not with dust when these two months have passed the dust does not act any more although pollinic crises may occur less intensively on account of there being less pollen

We have not often seen patients sensitive to hairs these always improve under treatment, provided that the ambient air is not too full of hairs In our service of Allergy in the Medical School the separation of various flour protein was obtained (proteose globuline gliadine and wheat glutenine also albumin and rye globuline) which have been administered as diagnostic and therapeutic means for asthmatic bakers we have even obtained pseudopodic reactions in them in general proteose and globuline were those substances which reacted most but the therapeutic results were relatively poor

ASTHMA AND RHINITIS CAUSED BY FUNGI

by

R ALEMANY VALL

The sensitivity may be limited exclusively to fungi or be a concomitant of other forms of sensitivity

1) *Sensitivity limited to fungi* It occurs frequently in patients living in damp surroundings (such as houses cellars parks etc) Rhinitis or asthma will appear although the best is to remove the patient injections may be administered of extracts of the fungi which had reacted on the skin and these injections give good results The cures must be repeated sufficiently The case of the patient is clear nasal reactions may be stimulated by contact with the respective fungus there always are nasal eosinophiles

2) *Sensitivity to both fungi and dust* in persons living in buildings housing cereals stores etc The desensitization with fungi and at times with dust is good the treatment must be frequently repeated

3) *Sensitivity to fungi and flour in bakers* The treatment is bad and may even produce opposite effects it is necesary that the patient should be removed because some of them cannot remain even a few hours in these surroundings we have always found there Mucor Penicillius etc If penicillin is administered by injection intensive asthmatic crisis may occur — although not necessarily nor always — and we have seen one with a subcutaneous emphysema

4) *Sensitivity to fungi in patients with bronchitis infections and asthma* These conditions do not respond to treatments with fungus-extracts but yield to bacterial vaccines upon the administration of penicillin extemporaneous asthmatic

reactions may still occur but they will fast disappear Skin reactions to fungi and bacteria may disappear in climates of high altitude and reappear or even develop into asthmatic crises when the patients go to lower places with a more damp climate than they were accustomed to

5) *Sensitivity to fungi in patients who exhibit small fibrous pulmonary lesions* with normal blood sedimentation and general well being an intensive and repeated asthma even without initial rhinitis The condition is improved by the administration of fungus-extracts tuberculin and similar products When the patient leaves the damp climate his asthma quickly disappears

6) *Sensitivity to fungi and dust in patients with small and reduced fibrous lesions* a clear case of rhinitis and asthma in damp houses with visible moisture on the paper of the walls although we did not always find fungi on these walls It will be necessary for the patient to change his living quarters because if not unpleasant — and even fatal — consequences may follow If the patient goes to live in well aired sunny houses with communication with free air the asthma will quickly disappear

Para allergic reactions will often occur

7) *Sensitivity to fungi in truly fibrous patients with a high sedimentation without any fever* positive lacto-gelification and inversion of the blood albumin globuline co-efficient heavy and rebellious asthma crises without initial rhinitis such patients cannot live in certain climates considered damp although sometimes there are no skin reactions to fungi These patients will improve when they live in temperate semi altitudinal climates in dry places protected from winds Treatment with fungi will give no results

In damp climates where humidity collects on account of local geographic conditions there will always be a higher percentage of asthmatic patients whose condition is due to fungi than in those in which there are open spaces and frequent winds

In country houses sufficiently far from stores of grain etc even if Mucor Penicillium Alternaria etc may be found their proportion will by far not be the same as those of rooms in city dwellings Fungi are abundant in granaries and stores etc We have even found them in operating rooms of modern hospitals

H J TEN CATE

Specific hyposensitization is a prolonged and expensive treatment It seems only justified to inhalant allergens which cannot sufficiently be eliminated like pollens mould spores house dust antigen and sometimes occupational allergens like cow hair and hay dust with farmers The results are often excellent especially with pollens and mould spores but some patients experience only partial or no benefit at all Before undertaking this treatment one should be quite sure of the existence of bronchial sensitization to the allergens chosen for desensitization

If the history corroborates the positive skin test evidence of bronchial sensitization exists

A positive skin reaction not confirmed by the history needs further investigation before starting hyposensitization treatment

A simple method to demonstrate bronchial sensitivity to inhaled allergens consists of inhalation of aerosolized allergenic extracts The effect can be demonstrated by recording the vital capacity before the procedure and several times afterwards at 4 minutes intervals

We obtained the following results on asthmatics when the history was not considered

Number of pat	Skin test	Inhalation results		Percentage	
		Positive	Negative	Positive	Negative
249	Strongly pos	147	102	59	41
183	Mildly pos	65	118	35 5	64 5
88	Negative	0	88	0	100

When the history regarding specific sensitizations was considered on patients with positive skin tests the following results were obtained

Number of pat with pos skin tests	Results of history	Inhalation results		Percentage	
		Positive	Negative	Positive	Negative
143	Positive	107	36	75	25
83	Doubtful	38	45	46	54
177	Negative	39	138	22	78

HOUSE DUST ALLERGEN(S) AND HYPOSENSITIZATION

by

KATE MAUNSELL

I HOUSE DUST ALLERGEN(S)

The pattern of bronchial asthma is constantly changing owing to phases in the degree of sensitivity of the individual and to environmental changes due to season and region or such irregular events as floods bombings and upheavals in daily life The composition of house dust reflects these environmental changes and is therefore in part responsible for the changing pattern of asthma

The material from which house dust is derived may be of intramural or extramural origin but house dust is not more dirt a dead mass of inert material It swarms with living organisms from 10 000 to several millions spores of fungi can be found in one gramme of dust the number of bacteria is equally large and mites too may live in house dust All these micro organisms either act as specific allergens themselves or by virtue of their enzymes break down complex organic matter into simpler compounds thus making or modifying house dust allergens

The materials which are broken down derive from building and furnishing materials of animal and plant origin such as horse hair (used not only for upholstery but also for ceilings in old houses) glue (the main component of sizes) feathers cotton wood and so on House dust further contains scales from man animals and insects and particles blown indoors or carried in on shoes or garments such as plant debris pollen and plant debris pollen and soil and also particles of ash carbon and tarry matter due to atmospheric pollution by fires Such is the conglomerate of house dust and several hypothesis are possible as to the origin of the house dust allergen(s)

1) House dust allergen(s) may be regarded as mixtures of specific allergen(s) deriving from these materials either in their natural state or after being processed by industry

2) In addition to this mixture there may be also one common substance which occurs during the phase of the breaking down of organic materials from different sources

Standardization

The lack of a good method of standardization is the major difficulty both in comparing samples of house dust and in estimating fractions

from any one single sample Rockwell et al (1947) found no correlation between the skin reacting substances and total nitrogen or phospho tungstic acid precipitating nitrogen Other authors have confirmed this Woodhouse (1954) recommended the Gel diffusion technique However the method of skin testing is still used in analyzing the potency of house dust although it lacks the precision essential in research The maximum of accuracy possible is obtained by intradermal skin titrations and determination of a threshold titre This is the reciprocal of the lowest dilution of any one extract to give a positive reaction Every fraction is tested against a standard fraction and a ratio established between the two The ratio of both threshold titres is referred to as test index It varies in different individuals to some extent Each sample was therefore tested on at least four dust sensitive individuals and the mean of the 4 test index figures obtained

House dust from different houses

It may be that the potency of house dust is influenced by the degree of humidity of the houses concerned and this again may depend on the soil on which the houses stand Such a possibility was suggested by Vallery Radot (1949) who observed the frequency of housedust allergy in persons living in houses built along the banks of the Seine Harsh (1952) noted that in the damp coastal areas of San Diego California with a relative humidity averaging 75 per cent the number of patients suffering from respiratory allergy to house dust was high In contradistinction in an extremely dry inland area below sea level with an abundant crop of pollen the main allergy was represented by pollen sensitivity He believed that humidity rendered house dust and possibly other inhalant allergens more allergenic In London which is built mainly on clay soil the onset of house dust allergy occurred more frequently in persons living in houses built on a relatively low level near waterways (Maunsell 1952)[1] Ordman (1952 1955) drew attention to the fact that in South Africa in respiratory allergy of the perennial type (which included house dust allergy but excluded pollen allergy) a combination of high atmospheric temperature and high relative humidity in constantly narrow range seemed to be the significant climate factor Further pursuing this question I obtained house dust from different parts of England all collected in September 1954 A wide variation in potency was shown confirming the results of Rockwell et al (1947) The strongest sample No 39 of the present series came from an extremely damp London house with cracked walls and damaged dampcourse built on a sloping clay soil The average test index of the crude dust antigen

[1] Confirmation of this observation came from Milan (Fior and Teseo 1955)

No 39 was 250 whereas the test index of dust from well preserved houses in different parts of England ranged only from 2—30

Sample 39 and 8 other samples have been examined for their mould content by Mr R R Davies and preliminary results showed that the total colonies of moulds grown per gramme of house dust on malt agar varied widely Sample 39 yielded 23,200 000 colonies of Penicillium whereas the 8 samples from drier houses in various parts of England yielded only from 60 000 to 1 100 000 colonies of Penicillium (R R Davies 1955) This result indicated that conditions favouring the growth of Penicillium favoured also the development of the dust allergens No evidence however has been obtained for regarding the Penicillium allergen as identical with the house dust allergen

Fractionation

In order to learn more about the active particles of housedust fractionation of single samples is essential

Mechanical fractionation separates the finer from the coarser particles of house dust As a result of gravity the smaller light particles float in the air a considerable time before reaching the ground According

TABLE I

Rate of fall of spherical particles of unit density in air at 20 degrees C and one atmosphere pressure

Reactivity	Diameter microns	Terminal velocity cm /sec
	0 2	0 000225
	0 3	0 0042
	0 5	0 0010
	1	0 0035
	2	0 0128
Strong	3	0 0275
	5	0 078
	10	0 30
	20	1 2
	30	2 7
	50	7 2
	100	25
	200	70
Weak	300	115
	500	200
	1000	385

from C N Davies (1954)

to Stokes law particles of one micron diameter fall at the rate of only 0 0035 cm per second whereas particles of about fifty microns diameter fall at the rate of 7 2 cm per second Unfortunately the smaller particles which float longer in the air and are therefore inhaled for a longer period are far more active than the larger ones This was shown by passing house dust through a sieve with a mesh of 76 microns diameter Extracts from the fraction passing the sieve produced much stronger skin reactions than fractions from the extracts retained by the sieve The particulate matter can also be graded into sizes by allowing the particles to settle in chloroform or benzene the heavier particles settling more quickly Again it was found that the lighter particles gave the stronger reactions (Table I)

Biochemical fractionation of house dust antigen is based first on the adsorption of the allergen of house dust by suitable adsorbents secondly on the retention of the active molecules by dialysing membranes and thirdly on their precipitation by acetone These properties have been made use of in the various methods of fractionation The method described by Rimington et al (1947 1952) followed the process outlined by Sutherland (1942) and carried it some stages further House dust was soaked with dilute ammonia and the extracts treated with sodium benzoate (20 grammes to 1 litre) The addition of hydrochloric acid (one part concentrated acid to five parts of water) produced a precipitate of benzoic acid which adsorbed the active material This was filtered of and the benzoic acid was dissolved by the action of acetone The dark material which was left as a precipitate could be dissolved in water and precipitated with aqueous acetone (25 to 80 per cent) The precipitate obtained at this stage was termed standard crude antigen

Further purification was obtained by dialysis against citric acid and the ash free material was again precipitated by acetone This purified material was highly active but protein tests were negative It contained 6 per cent nitrogen When this compound was hydrolysed with weak acid the carbohydrates were rapidly broken down and amino acids liberated Only when substantial liberation of amino acids occurred was the biological activity destroyed It was concluded that the polypeptide moiety was the essential part of the structure of the allergen

The same type of molecule (polysaccharides linked with polypeptides) has been found in the active fractions of fungal cultures as for example Penicillium (Stillwell et al 1947) and cotton (Cayton et al 1952)

Samples of house dust obtained from a firm of cleaners have been subjected to chromatography (Rimington et al 1947) Galactose was the only sugar composing the polysaccharide portion Partition chromatography to identify the amino-acids appearing on hydrolysis revealed the simple monoamino acids with the exception of histidine and

lysine The aromatic amino acids such as tyrosine and phenylalanine, were mostly absent

Chromatography has now been carried out also on house dust obtained from single houses The results have confirmed in the main the previous findings In some samples however other sugars—glucose and man nose—appeared apart from galactose

Partition chromatography using however butanol acetic acid water instead of collidine as the second solvent showed again that glutamic and astartic acids were present in all samples and that the aromatic amino acids such as phenylalanine and tyrosine were only found in a few samples

Considering the likelihood of wool and hair fibres being present in the original dust it is remarkable that arginine and cystine were found in traces only (Rimington) or else were absent (present series)

Inhibition test

The type of molecule described here resembles the blood group specific substances (Morgan and King 1943) which are in the tissues and secretions such as saliva of many animals and of human beings of group A and B Group specific factors inhibit the agglutination of red cells by the corresponding sera It seemed of interest to see whether the dust allergens would behave serologically in a way similar to the group specific factors

> Serial dilutions of one unit of serum in normal saline were mixed with one unit of standard crude antigen (10 mgm in 1 ml of normal saline) Control serial dilutions of one unit of serum in normal saline were mixed with one unit of the appropriate red cells in a citrate suspension and kept at 37 degrees centigrade for 30 minutes The titre was expressed as the reciprocal of the greatest dilution of the sera causing agglutination

Inhibition of the ABO agglutination by the dust allergen was shown although the inhibitory activity was of a lower order than that shown by the blood group specific factors (Rimington Stillwell Maunsell 1947) Binaghi (1950) confirmed this inhibition of red cell agglutination by house dust allergen(s) and reported this finding also in the case of related inhalants as e g cotton and feathers He believed that there was a close relationship between the strength of the inhibiting and the skin reacting properties of the allergenic solutions

The consequence of a hypothesis that house dust allergen is related to blood substances would be hyposensitization of dust allergic patients with human serum or horse serum Such hyposensitization with human

serum was started but was given up on account of the danger of homologous serum jaundice (Maunsell 1944) Horse serum injections appeared too dangerous Therefore the less harmful house dust is still chosen for hyposensitisation

II HYPOSENSITIZATION

In hyposensitization either extracts of house dust (Bencard) or crude dust antigen (Domogen Duncan) was given In the case of Domogen heat sterilisation was carried out as it had been shown that heating up to 100 degrees C on three successive days did not destroy the skin reacting properties There are certain advantages in the choice of house dust for immunization Even if the hypothesis of a common dust antigen is not accepted there is good reason to expect that such an extract will desensitise against feathers horse hair moulds and so on The risks so often evident in pollen immunization are practically non-existent in dust immunization Local reactions occur and may be painful but usually the infiltration dies down after one or two days Attacks of bronchial asthma are rare much rarer than after injections of bacterial vaccines

The subdermal hyposensitization follows the lines generally accepted in this form of therapy and has to be given over a period of 2 years Treatment with Domogen usually starts with 0 1 ml (dilution 1gm in 1000 ml) injections being increased by 0 1 ml up to 1 ml followed by 1 ml as maintenance doses at longer intervals up to 1—2 years

In cases treated the skin reactions decreased and often became negative Not always however did a negative skin reaction mean freedom from attacks

A blocking antibody developed during treatment It was however much weaker than the blocking pollen antibody occurring during hyposensitization The mechanisms of the two immunizations seem to differ It may be that the main effect of dust hyposensitization is ad sorption of the comparitively small molecule of the dust antigen to the larger molecule of the globulin antibody After some time the allergen may be freed again This would explain the short duration of the protection

70 per cent of cases treated enjoyed marked improvement during their treatment and half of them for many years later The others relapsed when treatment had subsided In evaluating results it should be borne in mind that the dust sensitive patient with asthma is also prone to infections and their adverse effects on the asthmatic subject and to emotional stimuli Hyposensitization with dust if successful controls only one side of the whole syndrome

In some cases it is possible to obtain better results from mixtures of

dusts with moulds or with weak bacterial vaccines and such combinations must be decided in connection with the patient s history In other cases it may be better to use a special source of dust again depending on the history In all cases however treatment should be combined with pre cautions and patients should realize the risk of inhaling air strongly polluted by house dust

SUMMARY

The potency of house dust varies in different houses The strongest sample came from an exceedingly damp house and had an excessively high content of Penicillium spores

Mechanical fractionation of house dust showed that the finer particles which float longer in the air were more active than the coarser

Biochemical fractionation demonstrated that the active molecule con sisted of a linkage of polypeptides with polysaccharides and that the activity resided in the polypeptide moiety

Chromatography showed that the polypeptides consisted mainly of the simpler monoamino acids and the carbohydrates mainly of galactose

The type of molecule resembled the blood group specific substances

The skin reacting properties of the crude dust antigen(s) were not decreased by heating to 100 degrees C for thirty minutes

70 per cent of cases found relief by hyposensitization with house dust extracts

Hyposensitization should be carried out over a period of several years and the best results may be obtained with house dust from a highly active source

Acknowledgements

I wish to express my thanks to than Messrs Duncan Flockhart and Company Edinburgh for assistance in the processing of house dust samples and chromatographic examinations Mr R R Davies Biology Department St Thomas Hospital London for allowing me to report the results of his mycological examinations and Professor C Rimington for his comments and criticism

References

BINAGHI R A (1950) *Annals of Allergy 8* 354

CAYTON H R. FURNESS G MAITLAND H B (1952) *Brit J Indust Med 9* 186

DAVIES C N (1954) *Dust is Dangerous London* Faber and Faber

DAVIES R R. (1955) Personal communication.

FIOR R TESEO L (1955) *Acta Allergol 9* 81

HARSH G F (1952) *Proceed ngs 1st Internat Con Allergy* Zürich 1951 Karger Basel N Y

MAUNSELL, K (1944) *Brit Med J* 236

— (1952) *Proceedings 1st Internat Con Allergy* Zürich 1951 Karger Basel N Y

MORGAN W T G KING H K (1943) *Biochem J 37* 640
ORDMAN D (1955) *S Afric Med J 29* 173
RIMINGTON C STILLWELL, D P MAUNSELL, K (1947) *Brit J exp Path 28* 309
RIMINGTON C MAUNSELL, K (1951) *Internat Arch Allergy 1* 115
ROCKWELL, G E THOMAS, J WITTICH F W (1947) *Ann Allergy 5*
STILLWELL, D E RIMINGTON C MAUNSELL, K (1947) *Brit J exp Path 28* 325
SUTHERLAND C (1942) *Brit Med J 11* 280
VALLERY RADOT PASTEUR (1949) *Allergie 48* 1 Expansion Scientifique Francaise Paris
WOODHOUSE (1954)

DISCUSSION

DESENSITIZING TREATMENT WITH DUST

by

R ALEMANY VALL

We used for purpose of the treatment ordinary commercial dust and that obtained from cleaning doormats on industrial premises we used however preferently the dust collected in the house of the patient himself especially in his bedroom We gave to the patient one or two inj ctions per week we never left him for 12 days without an injection The injections were diluted at the beginning and more concentrated afterward If the treatment is interrupted round the beginning the trouble will recur it does not happen however after five or six months The doses must be progressive and injected in different places the same dosis repeated cannot produce a cutaneous reaction but exercise a good influence The reactions usually diminish

Rhinorrhea is usually the first to diminish and disappear sneezing will last a little longer and will not come in fits but isolated and divided during the day the most permanent condition will be nasal obstruction

Skin reactions of inflammatory type appearing belatedly will give trouble to the patient but may improve very transitorily As results of the dust injections intercutaneous nodes may rarely sometimes appear they will have a clearly defined tendency to suppuration without fever or malaise on the contrary they exercise a beneficial influence on the illness because the rhinorrhea and asthma disappear in a few weeks We have seen the inflammatory nodes in ordinary asthmatic patients after intradermic injections of microbial vaccines with a good ulterior effect on the illness Their biopsy and microscopic examination (Dr Albantara) permitted us to see dispersed eosinophile cells together with neutrophile leucocytes having a tendency to suppuration

We have scattered the dust of these bedrooms in media for fungi both in general and banal and they did not produce any reaction on the patient s skin We used aqueous extracts or these extracts already concentrated in vacuum or those resulting from the evaporation by electric fan in colodion thimbles they were dialyzed with cellophane paper The portion called proteinic was separated from the hydrocarbonated exposing the watery extract to the action of a hydrochoric solution in boiling for 3 hours on different days

Other extracts had been exposed to a temperature of 55 −60 C during one hour and others even to 95 C for several hours the extract has kept in both cases its reactionary activity on the skin We have sometimes obtained a positive skin reaction both with the liquid which went through the cellophane and the one that did not We finally used for the extracts Seitz s filter with good skin reaction on the patient We proceeded with a pH of 7 5−8

Although the nitrogen value (index) does not show with absolute certainty the value of the extract our chemist from the Medical School had determined

the total nitrogen and proteic nitrogen by means of phosphotungstic acid there was as an average 1 241 mgm total nitrogen and 0 0560 mgm proteic nitrogen per c c in the dust found in the rooms of the patient

The standard dust of an industry working for the cleaning of rugs and mats in Barcelona contained 0 2800 mgm total nitrogen and 0 0420 mgm proteic nitrogen per c c

H J TEN CATE

Allergy to the house dust antigen is one of the main causes of asthmatic and rhinitis attacks in the Netherlands 112 out of 152 asthmatics examined at the Groningen University Clinic for Internal Medecine (Chest department) demonstrated positive skin reactions to allergens 100 out of them to house dust extract

35 normal persons out of 106 normal controls demonstrated positive skin tests 24 to house dust extract

91 asthmatics out of 169 asthmatic patients with a strongly positive skin test to house dust extract demonstrated a positive inhalation reaction to an aerosol of house dust extract which was inhaled (54 per cent)

25 patients out of 70 patients with mildly positive skin tests to house dust extract reacted positively after inhalation of the house dust extract (36 per cent)

In order to demonstrate the increasing bronchial tolerance during subcutaneous hyposensitization to house dust two hospitalized asthmatic patients were frequently exposed to house dust aerosol They received daily house dust extract injections in increasing amounts Blocking antibodies according to the technic of Kate Maunsell could be demonstrated

Pat	Date	House dust extract in mgm subcutaneous	Vit cap	House dust extract in mgm aerosolized	Decrease V t cap /	Blocking Antib
V R	8/8/ 1952	0	2150	30	30	Blocking index 0
	19/8	15	2500	36	9	
	29/8	42 5	2250	45	38	
	10/9	1087 5	2525	75	50	Blocking index 2
V V	6/8/52	0	2600	18	81	Blocking index 0
	16/8	1 05	3350	9	0	
	19/8	8 4	3300	30	15	
	2 /8	25	3300	30	9	
	30/8	91	3450	60	50	Blocking index 2—4
	5/9	466	3450	60	0	
	6/9	Discharged from hosp tal				
	14/10	1006	3500	30	12	
	25/11	1606	3450	69	11	(pregnant)

HOUSE DUST DESENSIBILIZATION

by

HELGE COLLDAHL

In a series of 387 patients with asthma bronchiale (from the allergy laboratory medical clinic Lund) the skin test was positive in 59 per cent The patients gave a positive reaction to dust in 41 per cent, to animal dander in 35 per cent, to different food stuffs in 31 per cent and to pollen in 19 per cent

Dust therefore is the antigen in the mentioned material that gives the highest percentage of positive skin reactions

When patients with a positive skin test inhale the antigen the provocation tests turned out positively in case of dust in 72 per cent in case of pollen in 59 per cent and in case of animal dander in 20 per cent

For two reasons therefore dust is an extremely important antigen for the troubles of asthmatic patients in Sweden A positive skin test for dust is more often a sign of hypersensitivity of clinical importance than a positive skin test for other antigens

When using different dust extracts very different results were obtained both by skin testing and provocation tests

The effect of hyposensitization is usually very good Long time treatment is essential When a strong dust extract (measured by skin titration and provocation tests) can be prepared from the patient s home the hyposensitization is carried out with this extract

References

COLLDAHL H *Acta Allergol V* 133 1952.
— *Acta Allergol V* 143 1952
— *Acta Allergol V* 154 1952

HOUSE DUST DESENSIBILIZATION

by

B SANCHEZ-CUENCA

It is a pleasure to me to co-operate to the sessions of this *International Round Table for the Therapy of Bronchial Asthma* with my personal experience in the hyposensibilizing treatment of those asthmatic patients sensitive to dust with its corresponding extracts The number of patients studied both by myself and my collaborators in my private office as well as in our Asthma Institute from the year 1945 amounts to 8420 among which 3640 were sensitive to dust This figure represents 43 2 per cent of the total number of asthmatic patients up to this day Of them 1721 had treatment only of dust extract and 1919 were treated with the extract alternated with an auto-vaccine of the germ or germs cultured from the nasal secretion In certain cases also from sputum

As a rule desensibilization proved effective and symptomatology gradually

receded when the doses of the allergenic active substance were increased But the simultaneous use of a nasal auto vaccine alternated with the dust extract proved even more effective The useful action of the vaccine in these cases may be ascribed to the elimination of the nasal allergic episodes of bacterial etiology which add to those produced by dust or perhaps because the infectious episodes are in favour of a pathogenetic action of the dust increasing the permeability of the mucous membrane to the allergen or acting as a non specific stimulant to the shockorgan this stimulant would have the effect of complementing the not sufficient allergenic action that is to say infection acting as a working factor in the allergic episode In dust nasal allergy specific desensibilization is much more effective than in asthma

5 per cent of our respiratory allergic to dust patients showed resistance to desensibilization disclosing their resistance in an increase of symptomatology after the extract injections In these cases they have been applied a protective treatment of Cortisone and ACTH While desensibilization went on and once a high dose of allergenic extract was reached we gradually suppressed the protective pharmacology at the same time reducing the extract doses down to a quantity which being effective could be borne by the patient without any Cortisone

Taking into account the different allergenic richness of house dust we have prepared 3 different types of extracts convenient to the 3 groups in which we have divided our patients

a) Rural or farms house dust very rich in organic matter mainly of animal origin

b) Marine or sea side dust especially rich in spores or fungi

c) Town or large city house dust, generally rich in those factors giving a particular character to the two previous ones On a base of reactivity common to the three extracts patients sensitive to dust fluctuate in their reactions to them according to their urban rural or sea side condition and we have taken advantage of these differences in their skin reactions to prescribe the corresponding extract treatment.

Specific desensibilization is necessarily long After two years of applying the maximum dose (1 c c of 4 per cent extract) we still continue giving a monthly injection of that dose for another year and even longer

When desensilization is effective the cutaneous activity diminishes which shows in the disappearance of pseudopodes in the intradermic test the hyperhemic halo also reduces but a round lump is still obtained which corresponds to a two crosses reaction In fact no real desensibilization is obtained but a process of hyposensibilization showing a lighter reactivity both of the skin and of the shockorgan

BACTERIAL VACCINE THERAPY*

by

A W FRANKLAND

There is considerable difference in opinion as to whether bacterial vaccines are of use in the infective type of asthma and whether any effect obtained is specific An autogenous bacterial vaccine apparently will give good results to many patients A control trial was carried out to see whether bacterial vaccines give specific help to infective asthmatics Patients were selected for the trial if the asthma was of a predominatingly infective type and in whom a bacterial vaccine would be expected to be helpful The vaccine was made from the organisms found from culture specimens of sputum or from a post nasal swab The organisms that were considered significant were streptococcus viridans or a non haemolytic streptococcus when in almost pure culture any pneumococcus or haemophilus influenzae or Friedlander s bacillus Each patient received the best available standard method of treatment and in addition received a bacterial vaccine or a control fluid Two doctors took part in the trial One of them believed that an autogenous bacterial vaccine gave specific help the other doctor believed that any help obtained was quite non specific in effect and that saline would give as good results A statistician placed the patients either in the vaccine group or control group by means of random number tables Each doctor reviewed his own cases for a year but not until the end of the trial did he know whether the patient had received a bacterial vaccine or carbol saline control

It was intended that each doctor should follow a hundred cases for one year One doctor followed up 89 patients and the other 95 patients A system of scoring was used for assessing the final overall result There were frequently several types of organisms in one vaccine A mixed stock vaccine was added to all the autogenous vaccines The strength of the vaccine was such that it contained 10 million per ml of each of the autogenous strains The control fluid was 0 5 per cent carbol saline

It was found that 54 per cent and 62 per cent (average 58 per cent) improved on the vaccine while 51 per cent and 54 per cent (average 52 5 per cent) improved on saline injections

(This article appeared more fully in the British Medical Journal (Oct 15 1955 p 941) *Autogenous bacterial vaccines in the treatment of asthma* by A W FRANKLAND W HOWARD HUGHES and R H GORRILL)

The trial showed that when an active interest is taken in an [illegible] patient half the patients for a period of a year will obtain [illegible] Any result reported that does not show a statistically signifi[illegible] provement on a figure of 50 per cent relieved does not support the val[illegible] any allegedly specific treatment It may also be pointed out that [illegible] *under the conditions of the experiment* was it shown that there was n[illegible] *difference between an autogenous vaccine therapy and saline injections* in the treatment of asthma It may yet be shown that bacterial vaccines under other conditions can give specific benefit in the treatment of asthma

SUMMARY

A controlled trial was carried out in 200 cases of infective asthma The patients were kept under observation for one year and given general supportive symptomatic treatment *It was found that regular injections* of an autogenous bacterial vaccine produced no greater benefit to asthmatic patients than similar injections of carbol saline Over 50 per cent obtained benefit from the treatment

DISCUSSION

HELGE COLLDAHL

According to the results reported by Dr Frankland one cannot expect any result from bacterial vaccine treatment

We have administered both stock vaccines and auto-vaccines to patients whose asthma is worse in connection with infections and we are under the impression that asthmatic troubles after infections are sometimes shorter and not so severe when vaccine therapy is given

In some few cases asthmatic troubles certainly become worse through vaccine treatment even if the doses are very small I therefore think it is difficult in all cases to deny a more specific effect from vaccine therapy

There is a group of patients who are dust sensitive but who rarely experience distress other than in connection with infections I think in these cases the most essential procedure is to give the patients hyposensitization treatment with dust extracts in order more or less to eliminate the chronic irritation in the bronchi caused by the dust sensitivity In this way the resistance to infections probably becomes greater

W J QUARLES VAN UFFORD

I was much impressed by the data supplied by Dr Frankland the more so as I had a much better opinion of vaccine therapy

The difficulty in evaluating a method of treatment in bronchial asthma is that in actual *treatment* either of the attack itself or of the sequelae of attacks we ask ourselves the question as to the point at which the drug to be administered will act so that we will be able to determine whether how rapidly to what extent and for what length of time the attack will be suppressed In doing so the question as to the cause of the attack is not taken into account In attempting to prevent attacks we should also ask ourselves whether it might be possible to identify one or several specific causes against which preventive measures might be taken This implies that the treatment of pollen asthma fungus asthma feather asthma etc with autovaccines should never be called a specific therapy

It is a different question whether autovaccine therapy may be regarded as a non *specific form of treatment such as pyretotherapy sulphur therapy gold therapy* etc etc

Dr Frankland has succeeded in showing that autovaccine therapy is not a useful non-specific form of treatment and also that bacteria frequently play no or no important part in the pathogenesis of attacks of asthma in a number of patients

As regards the use of non specific treatment with autovaccines I am as sceptical as Dr Frankland I have the impression however that it would be different if an autovaccine therapy — with regard to this matter I wish to point out that small

doses of the vaccines might be administered at regular intervals of 5 – 14 days (therefore this treatment is rather a method of maintaining immunity) — is combined with this form of treatment increasingly large doses being administered at about the same intervals and employed only in those cases in which it is definitely indicated

We believe this treatment to be indicated in the following cases

a) patients with bronchial asthma subject to continuous attacks of bronchitis (increased ESR, large number of neutrophilic leucocytes in the sputum an x ray picture suggesting a large number of infections)

b) patients with bronchial asthma showing a large number of focal infections in whom there apparently is a relationship between the infections and the attacks of asthma

c) patients with bronchial asthma liable to frequent attacks of dyspnoea following colds bronchitis etc (this group often includes children)

d) patients with bronchial asthma who do not show any intervals free of symptoms between attacks but continue to cough expectorate etc We treat the secondary bronchitis in these cases

e) patients with bronchial asthma showing markedly positive skin tests for one or several bacterial allergens whereas no definite focus (the possibility of a localization in the gall bladder tonsils or accessory sinuses of the nose being also borne in mind) could be detected

f) patients with emphysema and recurrent bronchitis

In preparing vaccines preparation of the ordinary autovaccine is combined with that of a stock vaccine the rule being that another vaccine is prepared when administration of the vaccine has failed to elicit any response or the condition of the patient remains unchanged after treatment has been continued for a few months Bacteria from the patient himself and stock bacteria are used in preparing the vaccine which is composed in accordance with the positive skin tests

Extremely good results may be anticipated when these indications are observed It should be borne in mind however that forms of asthma due to only one cause are hardly ever encountered The autovaccine will only be effective against the bacterial factor To obtain adequate results the other factors will often have to be treated as well

B SANCHEZ-CUENCA

We believe to have at present a fair experience of vaccine therapy on bronchial asthma Of our 8420 patients 4128 belong to the infective group and have been treated as basical therapy with bronchial autogene vaccines In answer to this therapy patients can be classified under four different groups

a) with a *brilliant* result corresponding to those whose sibilant symptoms remit after the first injections paroxisms cease expectoration disappears and the patient is for a long time in a position similar to normality and many times normal for the rest of his life if the treatment has been long enough

b) *good* when the result of the vaccine shows in the evident remission of the symptomatology in the disappearance of paroxisms diminishing of bronchial

secretion increase of their breathing capacity in repose but with persistency of a certain stage of dyspnoea after an effort disclosing the characteristics of an asthmatic dyspnoea even reaching the aspect of real asthma if the functional effort exceeds certain limits the functional recovery of these patients can be estimated at 60 – 70 per cent The disappearance of severe incidental catarrhs is a considerable advantage in their process

c) *middle* with a slight symtomatic relief hardly representing 10 – 20 per cent of recovery but with a fair reduction of serious bronchial attacks this anyway implies a considerable subjective improvement

d) *bad* we include in this group those without any relief and also those getting worse after the vaccine therapy

In our experience the first group represents 15 per cent the second group 45 per cent the third group 30 per cent and 10 per cent the fourth group

In these grades as a therapeutical answer very important facts are the duration of the process the existence of injuries to the bronchial wall the tendency to broncho pulmo sclerofibrosis the concomitant circulation alterations and the undiscriminating humoral conditions on which a clear immunologic answer depends

The composition of the vaccine may be very important to obtain better tolerance and the best useful effect The image in the culture plate which allows to evaluate to a certain extent the proportion of each germ in the sputum to be reproduced in the vaccine is a very misleading process The image in the plate corresponds to the sputum clot chosen by chance with the platinum handle We have always prefered to make tests of the germs through an intradermic injection to the patient and observe the intensity of the reactions but in the opposite way that is less quantity of those with a higher reaction and a larger quantity of those with a lighter reaction but nevertheless taking into the composition of the vaccine all those under culture on the agar blood plate We do not consider there is any *reasonable judgement on which to base the granting of any determined importance* to any kind of bacteria cultured from the breath exudes of the infective asthmatic We have denominated the vaccines prepared in this way compensated vaccines because the reactionary activity is compensated in them with the mass of bacteria

K WILKEN JENSEN

The results of Dr Frankland and co workers may be valid for adults but in my experience they are definitely wrong for children In the University hospital in Copenhagen we treat a lot of children with stock vaccine prepared from several hundreds of cultures from noses and throats of asthmatic children We regard the prognosis for the children with what we call infection asthma better than for the children with inhalation asthma The figures from my clinic show about 85 – 90 per cent of the asthmatic children symptomfree after a long time treatment with the stock vaccine of the Danish State Serum Institute Unfortunately I have no controls

FOOD ALLERGY

by

J F FARREPONS CÓ

Not only are we ignorant as yet of the internal mechanism of allergic diseases but the actual nature of the causes of allergy are also subject to considerable differences of opinion

Some authors believe that the effect of domestic dust is the primary producer of respiratory allergy while for others it is hardly if at all important The latter authors stress the action of moulds To a third group again various kinds of food constitute the most important allergenic agents And for yet another school of allergologists bacteria are chiefly responsible for the existence of asthma

This situation applies not only to our country but also to others In the United States for instance we find Rackemann believing that most asthmas are infectious but that food is not a factor of any importance In that same country on the other hand Rowe declared that in the majority of respiratory allergies the inhalatory and alimentary allergens are involved in the same proportion while bacteria have no effect

In France Belgium Holland Britain Italy and Spain opinions are also very divided For some authors the cause of allergic diseases is bacterial infection for others bacteria have no particular interest other causes being blamed

There are several reasons for this lack of agreement viz

I Lack of uniformity in diagnostic methods

A With respect to inhalatory allergies
1) Authors favouring the intradermal reaction
2) Authors favouring the dermal reaction
3) Diagnosis based only on passive transmission

B With respect to alimentary allergies
1) Authors favouring the intradermal reactions
2) Authors favouring the cutaneous reactions
3) Authors favouring diagnoses with only special diets
4) Authors favouring diagnoses based on pulsation hlanges and other procedures e g the microprecipitation test alimentary production of leukopenia etc

C With respect to bacterial allergies
1) Authors favouring the intradermal reaction
a) with extracts of whole bacteria
b) with polysaccharide fractions

2) Authors rejecting all allergic tests with bacteria
3) Authors favouring the Solis Cohen test (bacterial cultures from the patient s own blood cultures in infectious material from the same patient)

Yet another cutaneous reaction method widely used in England is the Prick method

Another group of difficulties arises from the non standardization of the extracts used in diagnosing

1) aqueous extracts for the intradermal reaction determining their contents of nitrogenum
2) water glycerin extracts for the dermal reaction
3) use of raw materials without extraction
4) use of pure Endo extracts (purified and concentrated extracts)
5) extracts determined by weight

It is obvious that the same investigator using those different extracts in the same patient must get similar results

I am at present making a survey of respiratory allergies with moulds (extracts of type 33 moulds) and to day we are diagnosing many more mould allergies than two years ago

In France Vallery Radot and Halpern made a study of the problem of dust allergy which having been fairly seldom diagnosed in that country some time ago now shows an incidence similar to that of other countries

A beginner in allergology who bases his knowledge on the experience of others will find his studies increasingly difficult owing to the variations in the way of life and food habits of the patients

An author writing on allergy will of course relate his own experiences and students searching for comprehensive knowledge are bound to go wrong if they attempt to copy exactly what they have learned from a foreign teacher whose experiences cannot of course be completely relied upon in all circumstances

Some time ago we had with us in Madrid and Barcelona Dr Albert H Rowe doubtless one of the world s best allergists In the latter town Dr Rowe gave some lectures entitled *Clinical Aspects of Food Allergy*

After listening to this scientist whose views were extremely valuable to us (Rowe said that the problem of allergy was generally speaking a matter of food) the only conclusion we could come to was that neither dust nor bacteria had any considerable significance

On the same day we listened to Dr Rowe at the Faculty of Medicine at Barcelona I received a folder containing some interesting words by Dr Chobot which I will copy here

There are two currents of opinion with respect to food allergy One, with its center in the West and Middle West believes that food is

an important cause which however can only become intense in the cycles of higher respiratory infections Another group including myself —continues Chobot— believe that although there exists food allergy that does not mean that it can develop its activity during the cycles of respiratory infection the important cause is the infection alone I do not favour the theory of any increase of alimentary hypersensitivity during high respiratory infection for my experience has taught me that alimentary hypersensitivity when high respiratory infection is present remains unchanged as long as the cause of shock is effective

In Cooke s work Dr Chobot author of the chapter on Alimentary allergy makes the following statements

1) Contrary to what is generally believed clinical alimentary allergies are infrequent

2) Allergies following the eating of certain foods (after one hour) may be diagnosed by immediate testing The patient generally knows the source of his allergy and has no difficulty in talking about it

3) Analysis of the delayed reaction is difficult both by means of cutaneous tests and by provoked alimentary tests As a rule only the last reactions can be determined by therapeutic proof

In his book on pediatric allergy Chobot summarizes the causes of asthma on the basis of his experience with 209 children of under 3 years old He finds that alimentary allergy (without inhalatory or bacterial allergy) was present in only 0 5 per cent of cases 3 per cent had alimentary allergy mixed with a bacterial one and 8 per cent had alimentary bacterial and inhalatory allergy combined On the other hand mixed bacterial and inhalatory allergy accounted for 48 per cent of cases

As against this Dr Rowe showed a survey comparing the four greatest causes of allergy the 1st very frequent the 2nd less frequent the 3rd least frequent and the 4th infrequent So far he classes food as 1 in bronchial asthma inhalatory causes also as 1 drugs and serums as 2 and infectious agents as 4 In the perennial type he classes food as 2—still very important therefore— inhalants as 1 (most important) drugs and serums as 4 and bacteria also as 4 (i e infrequent) Rowe s experiences in 1952 therefore mean that alimentary causes are preeminent in allergy These theories are supported by Vaughan Rinkel and Randolph but not by many other allergists including Cooke Feinberg Rackemann and others

Now let us suppose that both sides get the same therapeutic results say 70 per cent Then Rowe s group may get this percentage by the most specific diagnostics The second group may get the same result by using bacterial vaccines whose specificity is doubtful although the result is considerable Both groups of investigators arrive at the same goal but by different roads The Rowe group will eliminate the anaphy

lectic shock and produce alimentary micro-shocks The Cooke group will attain that equilibrium by producing non specific micro-shocks with bacterial vaccines

It may be more suitable to the allergist to belong to the *latter group* but none the less Rowe s technique is the more reliable in the long run

The effect of these techniques in our everyday work depends upon many factors The patient s mental state the time and patience which the allergist is able to devote to them the realization of a mutual interest on the part of doctor and patient all these and similar factors may make an important contribution Failing this the allergist may either join the other group, or prefer to adopt an eclectic attitude

Diagnosis of Food Allergy

It is not easy to diagnose a food allergy because of the slight validity of either cutaneous or intradermal tests for although they may appear to turn out positive it may also be that the patient is not so sensitive to the food that produces a positive effect as for a food whose effect is negative Therefore a diet based on cutaneous experiment is unreliable It is important for the allergist to know the order of frequency in which various foods provoke allergic attacks In a small manual which I wrote I gave the five different statistics including the order of frequency of the foods and the types of food that would most quickly and more slowly provoke attacks (Table 1) Naturally such a table of foods is of considerable interest for the study of alimentary causes of allergic disease and when a diet is drawn up a knowledge of the table also provides a new order of sequence to follow in any alimentary additions thereby avoiding fresh allergic troubles which will aggravate the patient s feelings of depression and hopelessness We must bear in mind that the patient pins his hopes on the doctor s knowledge and opinions and rarely knows anything about the effects of food Usually he has prejudices such as attaching undue importance to colds to defaecation or other organic movements women for instance would feel troubled while menstruating others again would worry about the weather etc

I will leave aside the various diagnostic procedures respecting allergenic foods and confine myself to giving our experiences in our own country Spain First there is the patient s clinical history to be written by the physician including questions of work habits place and condition of the home repugnance to any particular foods frequency of their ingestion etc It is a common thing to discover a hypersensitivity on the part of a patient of which he was completely unaware when talking about certain foods without a knowledge of any of them

TABLE 1

wheat	43 /	cabbage	4 8 /	rye	2 4 /
milk	21 4 /	nut	4 7 /	dry grapes	2 4 /
chocolate	21 /	rapeseed	4 5 /	veal	2 3 /
eggs	21 /	banana	4 4 /	plums	2 1 /
kidney beans	10 /	peas	4 2 /	radishes	2 1 /
tomato	10 /	peaches	4 /	garlic	2 1 /
fish	9 5 /	lamb	4 /	lemon	2 1 /
corn	7 6 /	apples	3 9 /	parsley	2 /
cauliflower	7 2 /	oats	3 8 /	shellfish	1 7 /
onion	7 2 /	asparagus	3 7 /	pepper	1 7 /
barley	6 4 /	artichokes	3 4 /	olives	1 5 /
rice	6 /	strawberries	3 2 /	oranges	1 2 /
celery	5 8 /	rabbit	3 /	herring	1 1 /
pork	5 4 /	carrots	3 /	chestnut	0 /
chicken	5 3 /	dry figs	2 8 /		
pears	5 2 /	beans	2 5 /		

As soon as this anamnesis is made—which generally informs us of an alimentary allergy although it may not appear to be the actual morbific agent—the patient is put on a basic therapeutic diet in order to attain an allergic equilibrium and establish a level For example

Lunch Milk of almonds
Rye bread
Apple marmalade

Dinner and supper
Rice soup made only of the meat of lamb
Toasted meat of lamb
Artichokes
Sweet potato
Grill
Lettuce
Olives
Pears and raw apples
Bread of almonds (turron)
100 mg B_2 and C vitamines daily

This diet—followed by the patient for 2 weeks—is useful also to determine aetiologic developments from other causes We do not mean that this diet will become completely non allergenic for sometimes patients will show a sensitivity to the meat of lamb or to almonds rice etc but the diet is a useful auxiliary to diagnosis As I mentioned before it is necessary to get proper control of bacterial and inhalatory causes in order to obtain fruitful results from this diet

In some cases the patient must be hospitalized in an air-conditioned ward (filtered air)

Having now established the allergenic equilibrium we now add the presumable allergens contained in so many important foods e g wheat milk and eggs Allergenic diagnosis to these three foods is made by means of the alimentary provocations verified at and before the patient s own doctor s

The proof of alimentary provocation takes place as follows The patient arrives at the doctor s after a good night s rest having neither smoked nor drunk and on an empty stomach The evening before he has taken a simple supper such as we prescribed in the above diet

At first the leukocytes will be counted twice while the patient is still fasting the average has to be taken After that the patient will take the food in question If it is wheat 3 or 4 spoonfuls of flour mixed with water with a sufficient quantity of water and sugar added and heated to a milk like soup

The proof with eggs consists in the ingestion of two boiled eggs or some raw eggs The milk proof drinking one glassfull is sufficient

The pulse rate must also be noted This done the food is taken the leukocytes counted every 20 minutes until one hour after its ingestion The pulse is taken again and the number of eosinophils counted Finally the doctor must carefully observe in the patient the following reactions

TABLE 2

1 sweat	9 stomach ache	17 weeping
2 anxiety	10 weight on the stomach	18 nasal stoppage
3 restlessness	11 ardour	19 asthma
4 uneasiness	12 pain at the uterus	20 urticaria
5 palpitations	13 diarrhoea	21 erythema
6 sickness	14 colic	22 itching
7 dizziness	15 itching	23 dermal oedema
8 vomiting	16 sneezing	

The concurrence of a decrease in the number of leukocytes down to 1000 acceleration of the pulse anxiety restlessness and general malaise etc *prove the unsuitability of the meal*

It is not difficult for the patient to diagnose himself at home and find out by the above method which foods are prejudicial to him The addition of the said foods must be in inverse order of sequence to that given in table 1

With the above measures one may obtain a treatment that does not get entangled with the bacterial and the inhalatory one My experience has taught me the necessity of intensifying our investigation of diagnostic

and therapeutic measures thus it may be possible to discover for instance that patients whose colds before treatment were extremely serious suffer far less from colds after adequate treatment Finally some patients who come to us diagnosed as bearers of infectious bronchitis may resist attacks of asthma thanks to the proper treatment for food allergy

As Rackemann said Not all that wheezes is allergy We may add Not all that wheezes is bronchitis — in the sense of classic bronchitis of an inflammatory nature and from a bacterial cause

Indeed we may also add Neither does bronchial silence mean absence of bronchitis In short although the symptomatology may appear absent on auscultation we may find ourselves faced with a patient with silent bronchitis who quite evidently requires treatment with adequate pharmacological measures

ELIMINATION DIET

by

C DE LIND VAN WIJNGAARDEN

Before dealing with my proper subject I will set out briefly the considerations that govern my diagnoses of allergic diseases and the treatment of my patients This also affords an opportunity to mention the names of those who were of great influence on my career namely Professor Rudolf Magnus and professor W Storm van Leeuwen who both lectured at this University

I am still grateful that my first schooling as Chief Assistant to Prof Rudolf Magnus was a pharmacological one Prof Storm van Leeuwen was my tutor on the subject of allergy

In his lectures on the treatment of diseases Rudolf Magnus distinguished between several types of therapy the main types being *symptomatic* and *causal* therapy

The underlying principle of the causal therapy is take away the cause of the diseases and you are cured In the field of allergy pollinosis might be mentioned as an example of a disease curable by *causal* therapy

In this connection we argue as follows The cause of the pollinosis is the pollen of some plant or other Prevent the pollen from getting into contact with the patient—in other words take away the cause—and the patient will be cured that is the symptoms disappear This is —of course—theoretically possible for instance if one goes to sea or as was the custom in Germany to Helgoland during the flowering of the grasses Another possibity is to arrange for the patient an allergen free room, for instance an air-conditioned room—so that he can remain in his own milieu In fact however this is no causal therapy for though the pollen is one of the causes of the disease the other cause is in the patient himself namely in his hypersensitivity So this example had better be referred to as a case of *elimination* therapy

It is even questionable whether causal therapy is possible Certainly —it may be said—it is possible if we make the patient insusceptible to pollen i e desensitize him Theoretically this train of thought is correct but it does not always hold in practice as is evident from the quantities of antihistaminics taken in the pollinosis season But even if the combination *elimination* and *desensibilization* would work, the therapy is always of the *causal* type For the restitutio ad integrim is not always reached Also the duration of the disease plays a part

We all know that pollinosis patients may finally develop hay asthma and that these asthma attacks may also occur at times when there are no more pollen in the air

So in this case neither the elimination therapy nor the desensibilization or the symptomatic therapy will cure the patient thoroughly At best they may give some improvement because the yearly stimulus does not occur

Finally also *psychic* factors will manifest themselves It is conceivable that a singer suffering from pollinosis feels herself threatened in her subsistence and that her mind gets fixed on this very point also outside the pollinosis season A generally known example is that of the man who gets pollinosis when he sees a painted rose That also the hormonal effects are of importance appears from the fact that pollinosis usually occurs at the age of puberty and may be disappear at a later age

Summarizing it may be said that even in the rather simple case of pollinosis with a distinct cause of the disease causal therapy is not easily possible

I have purposely enlarged on pollinosis because here is one specified allergen which could be eliminated

In the case of pure asthma bronchiale things are different It occurs only seldom that one distinct allergen can be designated as the cause When somebody is hyper sensitive to horses the same therapy as for pollinosis will mutatis mutandis apply remove the horse and the patient will recover Usually the patient knows that he is hyper sensitive to horses and in this case the skin test with horse—dander and hair—only serves to show that the patient is right

In other cases when the allergen say a cat is regularly present in the house the patient does not always know that the cat is the cause of his asthma One of my patients always got asthma when he was staying in Amsterdam with his parents in law In his own home he had never been troubled with it but for some time he had The cat hair skin test was positive On enquiry it appeared that he had taken a kitten with him from the parental home in Amsterdam to his dwelling When the cat had been removed the patient was quite well again So in this case the skin test was very valuable

With most asthmatic patients things are however more difficult If there should originally be one cause it has often worked already so long that even the elimination of the cause does not give recovery because also other factors have come into play Yet it may be expected that a great improvement may set in

Thus it is often seen that if a person who is hyper sensitive to house dust (which certainly applies to 90 per cent of the asthma patients) stays in an allergen free room—so removed from the cause— that

such a patient is freed from his asthmatic attacks as long as he remains in the room When this is not the case it should of course be ascertained what the cause may be and then it appears that it often lies in the *nutritional* field

And now we come to the question how to find out whether a given food is the cause or one of the causes of an asthmatic condition

The following points should here be taken into account

1) There is a pure allergy for one specified food which means that a minimum quantity gives a maximum reaction In such cases the patient himself usually knows that his attacks are due to a specified food and in this case the skin test only serves to prove that the patient is right In other cases it may be ascertained by accurate anamnesis whether a patient reacts to a specified food

Last Saturday for instance I was consulted by a patient in whose face an acute oedema manifested itself as soon as she tired herself when playing tennis When I asked her some more questions it appeared that since her early childhood she had not been able to stand fish or eggs Still this was not the cause of the present oedema as she carefully avoided to take any foods containing fish or egg

2) In other cases it can hardly be maintained that asthma manifesting itself after food has been taken is due to allergic causes Many patients suffering from asthma feel oppressed after dinner So there is a direct relation between dinner and oppression As in the Netherlands the potato is the only regular ingredient in hot meals while meat and vegetables being erved in varying sorts there would be every reason to think that these are cases of allergy to potatoes—the more so because there are no longer such feelings of oppression once the potato has been eliminated

The result of the intracutaneous skin test however is negative in by far the majority of cases Moreover there are no attacks of oppression after a dinner either when the patient considerably reduces his potato ration So this is contrary to the hyper sensitivity to eggs etc already referred to causing maximum reactions to minimum quantities

Therefore the conclusion is that the quantity of potatoes eaten produces the attack of oppression quite mechanically by obstructing the action of the diaphragma The situation becomes worse when fat gravy is taken at the same time For indeed this delays the emptying process of the stomach Such mechanical irritation can also occur after cabbage fat food and onions have been eaten It is therefore always important that these patients should be given easily digestible food

3) Further I wish to point to the fact that a certain combination of foodstuffs may cause an allergic reaction whereas such a reaction is not caused by any of these foodstuffs separately

Whenever it is considered desirable to find out whether there is any question of food allergy in a certain case skin tests and trial diets may serve the purpose at least in everyday practice

Skin tests (cutaneous and intra cutaneous) we always carry out a few skin tests namely for egg milk beef pork fish and shrimps (i e animal proteins) They are often supplemented by skin tests for cheese chocolate potato pulses and cabbage and by group reactions according to Bencard Whether any more tests are carried out depends on individual circumstances

For indeed there are serious drawbacks to such testing especially where children are concerned Children can indeed be subjected to a few tests but if they have to be repeated much psychic tension is the result I have children skin tested by an assistant during my absence so that when I come to see them later they will not be *frightened*

The matter is indeed, different in the case of adults They can stand many skin tests provided such tests are carried out with the necessary care I have done this for many years with various extracts such of those of Brocopharm Lifa Bencard and Barford of Copenhagen and in former days I also used the allergen-extracts of the Sachsische Serum werke which I have even tested for approval for many years

Without pretending that I should not mind doing without the skin tests I must say that it is often hard to get a clear picture of their results Of course I have seen amazing results in the course of the years (buck wheat egg milk currants spinach cabbage etc) but in many cases the problem arises whether a skin test produces a positive or a negative reaction Such doubtful cases make the job difficult Moreover I have often found that someone reacting to the widest variety of foodstuffs did not recover to any appreciable extent when on a proper diet Such observations are in perfect *disagreement* with the device *remove the cause and the patient is cured*

When the investigation into the influence of the food on the asthmatic attacks of the patient is carried out according to this device a complete recovery or at least a marked improvement in the condition of the patient should follow when he is deprived of all food

This brings us to the *diet therapy* which I am sure you all know My method is usually the following

Starvation for one or two days
then for two days rice boiled in water
after this rice vegetable butter and sugar
followed after two days by apple and apple sauce
and finally one vegetable variety is added every two day

So the *standard diet* is as follows

Morning bread and vegetable butter and meat sugar and apple and tea as a drink

Afternoon same

Evening meat rice sauce of vegetable butter vegetable (one variety) and apple

This standard diet can be continued for a long time and is subject to variations It is necessary for the patient to write down his daily diet and daily experiences in his food diary When the patient thinks he gets oppressed after eating a certain food this test should be repeated at least twice Different weekdays should be chosen i e Monday Wednesday and Friday and changes in the diet should never fall in the weekend The weekend breaks the normal rythm of life (weekend *asthma)*

Though I think that this is the best method for detecting the food allergen the disadvantage of the building up diet is that it is hard to practise in boarding houses Also in many households it makes high demands on the housewife Therefore as is generally known it may be useful to give an elimination diet by which one food or one group of foods is eliminated In my practice I act as follows

First for four weeks a perfectly *dairy free* and *egg free* diet even when the skin reactions to egg and milk are negative Also here the diet should be carefully noted down and it should be emphasized that butter milk and yoghurt and cheese are also milk products

When there is no clear recovery after a milk and egg free diet we change over to a *meat free* diet and then to a *carbo hydrate free* diet

Vegetables may be eliminated group by group In this way it may finally be found whether a certain food should be considered a harmful allergen

What value should now be attached to the diet in the case of asthma patients?

During my twenty five years of practice as an allergologist, and in fact during several more years in which I have been in close contact with the asthmatic clinical picture I found that the number of food allergens as the only clear cause of asthma in adults is very small compared to the large number of asthma patients for whom house dust is the harmful allergen mostly based on chronic bronchitis started in early childhood and on somato psychical influences This does not mean that I do not prescribe diets to my patients Of course asthma patients should only eat easily digestible food while for too heavy patients a reducing diet is indis pensable

DISCUSSION

R ALEMANY-VALL

We have seen in general, asthma associated with cutaneous lesions forming papules and eczemas or spots and prutitus of diffuse localization in which there were almost always small associated lesions of urticaria form type responding quickly to an anti allergic general alimentary regime (without bread of wheat milk eggs etc)

In other patients there were only cutaneous lesions to be found

In children with intolerance of or allergic regarding food exanthemas appeared over the whole body except generally on the cheeks Some of these children suffered from intensive and improductive initial cough sometimes even aphony to such a point that tracheotomies had to be practised In the same children this obstructive laryngeal picture was repeated afterward and responded to an injection of adrenalin In these children the same regime gave good results the asthma had disappeared whereas it was present continually on account of the immoderate consumption of harmful food.

We determine this general anti allergic regime on the basis of foodstuffs containing small quantities of proteins such as cabbages egg plants carrots artichokes beets chestnuts Brussels sprouts vegetal milk amino acids vitamins chicken or lamb jams cooked fruit olive oil and sobee

This regime was generally sufficient when it was not we eliminated the suspected foodstuffs (comparing the alimentary regime every day with the conditions of the lesions) and added others it was then a matter of much longer time to get good results

We made a few times Rinkel s tests for stimulating to action disturbance and have also taken a leucocyte count obtaining thereby some good results

J DUCHAINE

In my experience the use of a standardized diet encounters a great many obstacles And among these the most important are certainly the dietary habits of the people habits which can completely differ from one country to another

For instance in Belgium where wheat and potatoes are the two basic foods it is impossible to keep the patient strictly on a diet without cereals The best way of getting around these difficulties is to prescribe a diet which is palatable and pleasing enough and which contains only a minimum of those foods which the patient habitually eats For instance rye biscuits are given instead of bread grapefruit or pineapple instead of oranges or tangerines olive oil should be used for cooking instead of the usual peanut oil or beef fat. No eggs fish sea food or chocolate A few drops of tinned milk (i e milk that has been heated at a high temperature) are allowed and so are leafy vegetables and salads

If no striking results are obtained with this diet within 10 to 15 days the problem is reconsidered and some foods likely to be clinically significant like potatoes are struck out others are permitted according if possible to the personal tastes of the patient

ALBERT ROWE

The confirmation by Dr Farrerons-Có of the value of my elimination diets is very important Similar reports by allergists in other countries will be of great value

Our constant use of these diets for 30 years has indicated about equal importance of food and inhalant allergy with a minimum of infectant allergy in bronchial asthma Published statistics on nearly 3000 cases indicates food as the sole cause in 20 to 40 per cent in infants and young children 20 per cent in the young or midaged and 20—40 per cent in old age Food is often associated with inhalant allergy and inhalants alone cause about 20—40 per cent Drug allergy especially to aspirin must be remembered

This frequency of food allergy is greater than usually reported due in our opinion to several reasons

1) Errors and fallibility in skintesting are most important We test patients with 50 or more indicated foods by the scratch or puncture method

We look for large reactions indicating probable immdiate allergy But food allergy in broncho-nasal allergy is usually cumulative and chronic and negative indefinite or false reactions nearly always occur Thus a test negative diet usually fails Intradermal tests nearly always give false or questionable reactions in addition to those with the scratch test and are not done The clinical value of any reaction must be determined by injection tests but only in the symptomfree patient which may take 4—12 weeks with the proper diet

2) Because of this fallibility in skintesting our elimination diets excluding the common allergenic food with menus and recipes have been used for 30 years

3) Our success especially depends we believe on the recognition after 1930 of the importance of suspecting all cereals as well as milk eggs chocolate fish and other foods out of our elemination diets especially in bronchial asthma These diets as published with synthetic vitamins maintain the nutrition for long periods

4) If the diet is proper and foods are the sole cause improvement at times moderate will be noted in 1 to 2 weeks It should be continued with 100 per cent accuracy for 4—8 weeks until relief is assured With no relief allergy to some foods in the diet or to associated inhalants or rarely infectants must be assumed In regard to additional food allergy we suspect beef especially if milk allergy is probable Legumes potato and less often bacon chicken or some or all fruits and vegetables In our experience in the U S A potato allergy is infrequent Potato is eaten 1 to 2 times a day at times in large amounts by most Americans But not as much as in northern Europe It may be that its apparent frequency will decrease with more frequent study of allergy to all cereals as well as to milk eggs or other eliminated foods Minimal diets thus may be utilized even one with lamb or beef tapioc cooked with sugar and caramel sugar up to 80 grams a day salt water

and synthetic vitamins With definite relief foods one every 3 – 5 days are added excluding those which reproduce symptoms *Enough of these foods must be eaten to maintain weight*

5) Our long recognition of exaggeration of food allergy in the winter months *also often causing recurrent colds and coughs with no asthma and improvement* of food allergy in dry inland or heigh areas must be remembered

Finally the classical history of bronchial asthma due to food allergy especially in young childhood is restored It was recently republished in *Progress in Allergy* edited by Kallos in 1952 in an article on bronchial asthma due to food allergy in which my elimination diets and other advised treatment are also *included* Regular attacks occur usually preceded with nasal symptoms suggesting infection but due to food allergy

Temporary exhaustion of reacting bodies explains interim relief though aller genic foods are eaten daily During summers slight symptoms may allow libera lized diets The strict cereal free elimination diet usually is again necessary in the autumn until late spring Fever with vomiting due to food allergy may occur Similar symptoms with above relief occur in adults and old age though asthma *usually is more persistant*

Food allergy therefore must be studied when recurrent or persistant asthma occurs usually exaggerated in autumn to late spring A diethistory of food dislikes or *disagreements* and seasonal and *geographic variations suggest foods If large* scratch reactions or a suggestive history to specific foods occurs their elemination may give relief Usually skin reactions are absent or questionable justifying our cereal free elimination diet Inhalant or rare infectant allergies always must be remembered Along with control of food and inhalant allergies symptomatic *relief with usual drugs but never opiate demoral or sedatives* and if necessary cortisone and ACTH is indicated These can be reduced or excluded as the brochonazal symptoms gradually are relieved with anti allergic therapy

With the free use of elemination diets the importance of food allergy in broncho nasal and other manifestations of clinical allergy will become evident As with any other diet or test elimination diets must be used for more than a few months and on more than a few patients to attain necessary experience and facility in their use

BRONCHIAL ASTHMA - ASPECIFIC THERAPY

by

FRED W WITTICH

A large proportion of cases of bronchial asthma have an existing hyper sensitiveness of the bronchial mucosa or musculature in which the latter structures react to a variety of stimuli such as cold wind dust excitement and fatigue [11] This condition of hypersensitiveness should be regarded as a pathergy rather than an allergy

In the broad sense aspecific treatment of the patient with bronchial asthma consists of those nonallergic measures which correct the abnormal alterations in physiology This would include all symptomatic treatment, such as drugs and operative procedures

Therefore with all methods of specific and symptomatic adjuncts as discussed at this symposium the writer s paper will deal exclusively with these aspecific agents which have been considered as conferring some degree of immunity in an indirect manner

The employment of such aspecific measures without first determining and adjusting specific etiologic factors as much as is practical and possible is inexcusable

At the present time the increasing improvement of our diagnostic procedures warrants the abandonment of aspecific measures formerly proposed when we were groping for some beneficial remedy which would be a shortcut to proper immunologic methods and when the proper approach to diagnostic procedures for many reasons were markedly limited A comparatively few aspecific measures in the present day therapy of asthma are warranted

There are however frequent occasions when specific and symptomatic measures must be complemented in order to give the patient some comfort and relief At the onset and for some time there may be difficulty in determining the specific causes of symptoms and when known, they as well as the complicating changes may offer considerable difficulty to manage

Aspecific measures which have been used with some relief to the patient with bronchial asthma include tuberculin nonspecific proteins such as milk and peptones and shock therapy artificial fever colloidal sulfur the use of endocrines particularly ACTH and cortisone vitamin preparations physiotherapy psychotherapy roentgen ray therapy bronchoscopy and iodized oil surgical procedures, digestant chemicals and enzymes corrective fluid and electrolyte metabolism urinary

proteose ionized air et cetera All of these methods have their advocates but time and trial have eliminated a number of them as valueless A few of the most important will be mentioned

Surgical Procedures Any surgical methods to inhibit the autonomic nervous system s influence on asthma have been mainly partial and temporary [3] Such procedures may cause various annoying complicating nervous phenomena Stellectomy after estimation of a blocking anes thetic agent seems to be the method of choice Other procedures such as unilateral extirpation of the cervical sympathetic ganglia vagus section and resection of the posterior pulmonary plexus by and large have been disappointing

Digestant Chemicals and Enzymes These have been used for aiding food digestion It is well known that gastrointestinal disturbances may be a precipitating factor of asthma Nitrohydrochloric acid or urea nitrate may favourably influence these factors Citric acid [2] in 4—16 cc doses of a 25 per cent solution in water or lemonade sipped with the meals may be tried The digestive enzymes pepsin and pancreatin are helpful Coated tablets of Cotazym (Organon) are preferred where di gestive disturbances are present as they do not contain bile salts which act as a laxative

Fluid and Electrolyte Metabolism In 1940 Stoesser and Cooke [9, 10] reported the importance of electrolyte and water exchange in bronchial asthma Sheldon [8] and his associates reported cases where asthma could be induced or aborted at will when observed in regard to water and sodium metabolism regardless of whether they were initiated by foods or by inhalant allergens They noted the asthma attacks were associated with considerable loss of body fluid and increase in the urinary sodium and that the loss of sodium through the urine in direct relation to the body water loss Harsh and Donovan [4] observed the effect of the wide variation in potassium and sodium intake in children with asthma Their observations which were carefully controlled by ingestion experi ments demonstrated that a high sodium intake increased the amount of asthma whereas high potassium intake had little or no effect Experi ments now being carried on by the author in collaboration with others indicate that besides the sodium and potassium metabolism to be con sidered in allergies there is also that of calcium and other electrolytes

Urbach and Willheim [12] made chemical studies of a similar nature when endeavoring to ascertain the allergic action of certain organic acids They showed that the symptoms were the result of anions They em phasized the importance of experimental testing in these cases since patients are also known to be allergic to a number of cations It must be kept in mind that foods containing acids such as vinegar or acetic acid may produce allergic symptoms or even the acid in sour apples

may be a factor (wine oranges lemons pickles et cetera) Negative skin tests to these foods when shown to produce symptoms by ingestion may be the result of the acid or alkalines contained therein

Heretofore observations of electrolytes in the treatment of allergic states have been on sodium restriction and increased potassium intake The author s experiments in collaboration with Dr Irvin Moore have shown that electrolyte abnormalities are found in those allergic patients where there is more or less prolonged dehydration due to lack of fluid intake or loss of fluids as in the profusely weeping eczemas particularly in children and which is frequently complicated by water loss due to diarrhea

In angioedema during the swelling as a result of escape of fluid into the perivascular or extracellular compartment there is a loss of K Even between attacks the serum Na values in mEq is a maximum normal or slightly above while the K is usually the minimum normal or less During the attacks there is a definite K depletion

In severe acute and generalized infantile eczema with weeping particularly if associated with diarrhoea there is a considerable loss of potassium Following a low blood potassium level in these cases either Butler s Darrow s or Baxter s Electrolyte Solution No 2 should be given intravenously This may be lifesaving and result in restoration of the skin from an irreversible condition under other anti allergic measures alone

Patients suffering from exfoliative dermatitis with marked edema of the subcutaneous tissues and exudation lose electrolytes through fluid loss and K is frequently found low in these patients A repair solution containing potassium and calcium should be used in these cases

In status asthmaticus or severe intractable asthma the patient is usually dehydrated from lack of intake of fluids by mouth Sweating increases this dehydration Hydration is customary by intravenous introduction of 5 per cent glucose in normal saline or distilled water There is no advantage in using larger concentrations of glucose particularly when the patient is receiving ACTH or cortisone A potassium deficiency in these patients may seriously disturb the Na/K ratio Calcium which diminishes capillary permeability should be increased more than that contained in the present repair solutions Chloride values are usually found slightly in excess in severe asthmas and angioedema and should be at a minimum Morphologic changes in magnesium deficiency include increased vascular permeability myocardial fibrosis neurologic degenerative changes and the nephrotic syndrome Like potassium magnesium is mainly an intracellular substance The serum concentration is quite low 1 4 to 2 5 mEq/L Due to hemoconcentration seen in severe dehydration as in severe bronchial asthma there is a comparatively high

serum magnesium Serum levels above 6 mEq/L are associated with progressive depression of cardiac conduction and neuromuscular activity which is to be avoided in severe bronchial asthma with myocardial damage The serum level of magnesium should therefore be comparatively low Repair solutions more suitable are proposed for these cases as follows Travert 10 per cent Electrolyte No 2 Darrow s Solution and Butler s Solution have been used successfully Aminophylline and epinephrine can be added to these repair solutions

Ethylhydrocupreine has been used in asthma with favourable results

Alcohol When aminophylline fails to give relief Brown[1] recommends the intravenous administration of ethyl alcohol 5 per cent in glucose saline To the alcohol solution 0 10 to 0 50 ml of 1 1000 epinephrine should be used The drip is regulated to 80 to 120 drops per minute until the patient shows a pink flush or mild excitement When the patient falls asleep the rate of injection is reduced to 60 to 80 drops per minute The procedure requires about two hours

Urinary Proteose In the past there has been much discussion of urinary proteose with some advocates Time has shown this substance to be of little value and the results are comparable to those of peptone injections

Ionized Air Inhalations These were tried by Landsman[5] to counteract the effect of weather changes on the asthmatic patient and were claimed to show a high incidence of improvement

Roentgen Therapy This has been used more in the past than it is at present It should be applied only by the roentgenologist who is familiar with its technique The author has seen cases in which patients with progressive intrinsic asthma obtained considerable relief for some time from roentgen therapy when all other measures failed to help The advent of ACTH and cortisone in this type of patient has practically supplanted other methods of treatment

Artificial Fever Therapy The use of remissive therapy or treatment aimed at producing a prolonged symptom free interval particularly in patients who have received cortisone and ACTH for long periods with decreasing effectiveness or where side reactions develop from the use of these hormones should be considered Frequently the use of artificial fever is the most effective method of inducing a remission Typhoid bacillus vaccine such as Kirk s Typhoid Vaccine * given intravenously two million units at the first injection and increased by 50 to 100 per cent depending upon whether a rectal temperature of 101 degrees Fahrenheit or higher has been produced is helpful

Another effective fever producing agent is Piromen[R] (Travenol) a

* Kirk Manufacturing Company New York, N Y This contains no Paratyphoid A or B organisms which may cause shock

sterile nonprotein and nonantigenic bacterial polysaccharide in a stable aqueous colloidal dispersion for parenteral use The product is marketed in a bottle containing 10 gamma per cc The initial dose intravenously is 0 05 cc (0 5 gamma) which is increased until an adequate fever response is induced

Physiologically Directed Therapy Various adjunctive physiotherapy procedures have been advocated in the treatment of asthma Diathermy may be of temporary benefit where heat and sweating are helpful Treating children with ultraviolet rays may be beneficial by improving the general health

Measures Used to Aid in Restoration of Impaired Function (in patients with status asthmaticus and those with severe protracted bronchospasm) These procedures vary with the individual patient and may consist of intermittent or continuous oxygen inhalations Thirty to 50 per cent oxygen may be given by oxygen tent double bent tube or nasal catheter to relieve anoxia and functional pulmonary emphysema Intermittent administration of the same strengths of oxygen are safer where there is considerable advanced emphysema

Helium oxygen inhalation in the proportion of 80 per cent helium to 20 per cent oxygen is used to aid alveolar ventilation but the studies of Schiller et al[7] failed to show any clear cut difference between air and a mixture of 80 per cent helium and 20 per cent oxygen In eight severely ill patients these authors observed no significant change in the expiratory reserve volume the inspiratory capacity the vital capacity or the speed of flow during the measurement of vital capacity

Intermittent or continuous pressure is used to increase the diameter of the bronchi and maintain adequate ventilation It may be used also in pulmonary edema Intermittent pressure breathing is also used with negative pressure in expiration By this means mucous plugs may be eliminated where coughing was ineffective

These procedures may be accompanied by the continuous use of nebulizing or bronchodilator solutions singly or in combinations of which there are several on the market

Iodides have a nonspecific action by preventing the mucus from becoming dry and adherent to the bronchial wall

Patients refractory to epinephrine and aminophylline get considerable relief by the administration of 50 mgm of Demerol[R] intramuscularly every six hours for three or four days only Dilaudid subcutaneously in 1 mg doses every six or eight hours for three or four days may relieve a protracted bronchospasm Both narcotics are habit forming and should be used only where the usual bronchodilators fail

Bronchoscopy is used frequently as a diagnostic procedure in asthma and simulating conditions The removal of inspissated sputum by means

of the bronchoscope may relieve a status asthmaticus The discomforts and damages from the use of iodized oil in connection with the broncho scope exclude its possible benefits

Prickman and Moersch[6] point out that bronchostenosis frequently results in asthma resulting from inflammatory changes This narrowing of the lumen retards the flow of air and contributes to the retention of secretions Subsequent extensive observations by Moersch and his co workers continue to substantiate the value of bronchoscopy in selected cases

The subjects of physicotherapy the treatment of emphysema and psychotherapy as aspecific measures are omitted in this discussion be cause they will be presented by able authorities participating in this program to morrow

Ref rences

1 BROWN A G III BLANTON W B Therapeutic effects of am nophylline in asthma *South M J 33* 1184 1940
2 BROWN O H Further studies n treatment of food sensitizat on with digestant and citric acid *J Allergy 1* 180 1930
3 FEINBERG SAMUEL M *Allergy in practice* Chicago The Year Book Publishers 1946 P 549
4 HARSH G F DONOVAN P B The effect of wide variations in potass um and sodium intake in asthmatic children *J Allergy 13* 105 1942
5 LANDSMAN I E Ionized air in bronchial asthma *Sovet vrach ga* p .27 1935
6 PRICKMAN L E MOERSCH H J Bronchostenosis complicating allergic and infectious asthma *Proc Staff M et Mayo Clin 16* 305 1941
7 SCHILLER IRVING W LOWELL FRANCIS C LYNCH MARY T FRANKLIN WILLIAM The effect of helium-oxygen mixtures on pumonary function in asthmatic patients *J Allergy 26* 11 1955
8 SHELDON J H HOWES STUART G Observations on total water and sodium exchanges in asthmat c patients *J Allergy 10* 1 1939
9 STOESSER A V COOKE M M Electrolyte and water exchange in bronchial asthma with emphasis on the influence of pitressin *J Allergy 10* 557 1940
10 STOESSER A V COOKE M M Possible relation between electrolyte balance and bronchial asthma *Am J D s Child 56* 943 1938
11 URBACH E GOTTLIEB P *Allergy* .d ed New York Grune and Stratton 1946 P 565
12 URBACH E WILLHEIM R Quoted by E URBACH and P M GOTTLIEB *Allergy* New York Grune and Stratton 1943 P 381

DISCUSSION

R ALEMANY VALL

We can consider as desensitizing treatments

1) Vitamin A in massive doses administered orally and taken at regular inter valls by itself it will cause the disappearance of coryzas of non-specific allergic type

2) Gamma globuline injections which produce perhaps an earlier effect in rhinitis also

3) Azo-proteic histamine in cases of nasal colds the origin of which is unknown and in which there is a principal or secundary physical factor They contribute for instance to the action of the microbial vaccines

4) Thyreoidin in medium or large doses lowers the sensitivity to colds and therefore to catarrhs in certain patients of normal appearance

5) Pyromen (hydrocarbonated portion of certain pneumococci) not adminis tered *intravenously which is generally not tolerated, but sub-cutaneously* in sufficiently regular injections for infections type rhinitis and asthma

6) Pregnandiol extracted from the urine of the patients by Aswood Jones procedure Intradermic injections every 3—5 days without taking into account the epoch of intermenstrual period specially in crises asthmatiques of premen strual appearance

We think, that the effect although specific to a certain extent, is really non specific similar to that of azo-proteic histamine acting upon the premenstrual tension of primordial histaminic influence

7) The premenstrual serum of the patient produces sometimes good results we have even seen two cases of premenstrual facial eczema treated with folliculin with good results

8) Nitrogenized mustards in small doses only three injections on alternate days their action being similar to that of ACTH they are not dangerous in such small doses It is sometimes necessary to administer antibiotics before and after the treatment

9) Tuberculin or similar products which although they may act non specifically usually produce good effects at least at the beginning of the cure in those asthma cases in which a small pulmonar fibrosis is present and they act afterward as specific agents

E WOLFER BIANCHI

It would not be right not to mention the use of Iodine Pepton in the non specific desenzitation in the treatment of asthma

I remember the names of Auld and Pollitzer using Pepton alone with intra muscular injections and Cantonnet using a certain preparation of Iodine Pepton which he calls Desensibilisine I use myself since 20 years the Iodine Pepton of the french pharmacopoe with intramuscular injections every 5—7 days beginning with a dilution of 1 5 and increasing the dosage I can assure you that a great part of asthmatic patients react very well and that the curative effect is a highly good one

THERAPY BY HOME AND FAMILY EDUCATION

by

ZAIDA ERIKSSON LIHR

The outstanding advances of recent medicine are of great value to the allergologist of to day in determining what stress it is that has changed the reaction of a normal person or a person with a latent allergy to manifest allergy (Fig 1) The specific sensitivity can be defined through skin and provocation tests The focal site of infections causing an allergy is nowadays not too difficult to localize The determination of functional sufficiency or insufficiency of the hormones still render us some difficulties which seem however easier to solve day by day thanks to the new methods of hormone titration Last but not least in medicine to day the ever increasing understanding of the psychic stress as a cause of allergy is well worth mentioning

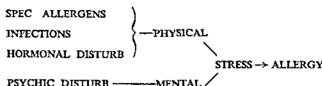


Fig 1

The means of combating the pathological processes found in the allergic organism are also greatly improved I only like to mention specific and unspecific desensitizing the elimination of focal infections new and effective antibiotics and the long row of excellent hormones Accordingly the allergologist can with a great deal more confidence than before terminate the patient s hospitalization and transfer him to homecare But at this point the physician soon enough observes that new difficulties arise The patient who quickly recovered in the hospital often at home soon developes new symptoms and has to return for treatment

Yet the doctor had scrupulously tried to unravel the case had questioned the patient on his home and working-conditions and warned him of the specific allergens he should avoid He even had as a parting gift pressed into his hand a pamphlet explaining causes and cures for his allergy As a result the patient who is allergic to horsehair conscientiously avoids visiting the stables but unfortunately sleeps every

night on a horsehair mattress which causes him asthma attacks The patient who is allergic to cowshair and sheepswool thoroughly avoids these animals but at home during the day walks on a rug woven with cowshair and sleeps in a bed next to a woolen wall rug Another patient lives in a damp house by the sea with mold growing under the wall papers and in the cracks in the floor and even in her pillow which she has neglected to clean

The allergologist sacrifices much time and work in examining his patient and treating him But how often has all this work been in vain? The patient has not understood the doctor has not been able to co operate has forgotten We write pamphlets and have them printed to enlighten the patient and his family Such pamphlets are already available in every country where there is advanced allergy work But a pamphlet quickly becomes out of date Let us remember all the new chemical substances which are used every day in hosiery and clothing in materials foods medicines and in the different industries and we realize that such a pamphlet can stay up to date only for a certain time If such a great change in substances did not occur practically every day I would suggest to the International Association of Allergologists to nominate a committee to draw up these pamphlets and to distribute them in millions all over the world Unfortunately this is not possible—each country must have its own pamphlets which are in accordance to the life and habits of its population Such a pamphlet is of considerable help

What else can be done to educate the allergic patient and his family? Patients Clubs are of great importance The patients receive psychological satisfaction in being able to discuss with one another the nature of their sufferings and distresses They want to feel that they are worthy of consideration and do not want to be forsaken or misunderstood as allergic patients often are Short lectures on allergy with following discussions are very much enjoyed in these meetings in which also the patients family eagerly partake because of their wish to learn to understand their suffering relatives These lectures can be held by doctors nurses and also by the patients themselves Such meetings of the allergy patients club in Helsinki gather thousands of interested and grateful patients and their relatives and seem to be a great event both from the educational and social point of view

An educational program on allergy must be out lined by someone who has time and interest enough to devote to it This person must also be trained to keep both ears and eyes open for everything new that happens in the field of allergy This is not an easy task I would like to mention that recently we were consulted on numerous current cases of hives eczema and asthma for which it was difficult to find a cause Finally it was discovered that the underlying cause was the new winter

turnip rape plant (Brassica Rapa Oleifera) which was recently started to cultivate in our country and the oil of which is used in cooking salad dressings mayonnaise etc and specially in the production of margarine This Spring a great many men complained of itching and eczema caused by their new clothes It was established that this was due to a new quality of unbleached tricolette underclothing in which the cotton seed residuum caused allergy The same reason for allergy was noticed in cases where the patient used unbleached bed linen One of the severest allergies is sensitiveness to asperin which may cause asthma constitutional shock even death Regardless of our constant warnings to patients of the great danger in using asperin unexpected states of shock were evidenced Investigations brought forth that head ache powders contained under a different name a substance related to asperin All these facts must be registered in an *allergy black book* which serves the doctors as a warner and the patients as an educator But who has the time and the energy to collect all this data? The prac ticing allergologist does not have time for it Besides this work requires a person who is familiar with the different details of the homes and their surroundings and who is able to complete this knowledge with studies of the new materials modern industry has brought to our homes and our working places especially in foods medicines cleaning agents paints and those used in home decorating

In Helsinki at the Hospital for Allergic Diseases—a hospital specialized in the treatment of all different allergies and which at present has only 40 beds but an out patient department which during last year had 16 500 visits—we have trained for this purpose a special personnel to aid the doctors These allergy nurses who have a training of a Social nurse and know all about case work not only keep their eyes open for new allergens but also personally study each new hospital case as a help to the doctor

When a patient is admitted to the hospital the allergy nurse fills in a special home page of the patient s case history The patient is re quested to give as accurate a description of his home conditions as possible the number and size of the rooms the number of family members who live in these rooms also the age of the family members what type of bed do they have the filling of mattresses and pillows is furniture new or old upholstered or not what rugs there are on the floors what pets or farm animals what flowers what working-conditions etc This information gives the physician a good background for his studies and allows him to compare the history with the results obtained from skin testing and other examinations If we deal with a child a thorough inquiry is made into the earliest childhood and its diseases In women the menarche and climacterium are investigated thus giving a

basis for hormonal studies During the patient s hospitalization the allergy nurse pays daily attention to the patient discusses further with him the home working and economical conditions and becomes thus acquainted with the patient and his personal physical and psychic stress

It seems easier for the patient to open his heart and tell his manifold troubles to the allergy nurse than to the doctor After the examination and the treatment of the patient is completed and the doctor has done his utmost to give the patient the necessary medications and advice for home-care the patient is referred back to the allergy nurse who has won the patient s confidence The allergy nurse goes once more through the case history compares known home facts to results obtained from examinations and endeavors to make a further dive into the environmental situation of the patient She explains about materials containing wool feathers and different animal hair she advises the patient how to avoid dust in the home she names foods to be avoided and so on When discharged from the hospital the patient is requested to report to the allergy nurse once a month and more often in case his health has not improved The nurse then discusses the situation with the treating physician keeps in contact with the patient and calls him back when necessary

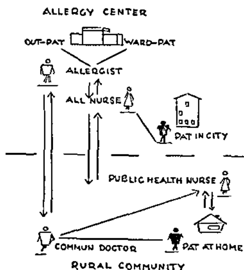


Fig 2

Finland is very fortunate to have a governmental Public Health Nursing system developed throughout the whole country In every rural community there is for the community doctor s assistance a Public Health Center with a Public Health nurse and a mid wife to every 4000 inhabitants If our patients are from the city of Helsinki and their homes are visited by the allergy nurses they are referred back to the out patient department of the Allergy Hospital if needed In case the patient living outside the Capital needs personal care or a visit to the home he is advised to turn to his community doctor or Public Health nurse who are in contact with the allergy nurse and the physicians at the Hospital for Allergic Diseases (Fig 2) In this way we have developed a system for home education study and care for the

allergic patient and which system seems to us to be of utmost importance Thousands of letters circulate yearly between the hospital and the patients They save the patient useless calls to the doctor but promote them when they are really needed These letters combined with necessary general pamphlets provide the patient allround home education on allergy and make him and his family familiar with his personal type of disease It also allows the hospital a follow up of the patient which seems to be of great value

SUMMARY

In the social department of the Hospital for Allergic Diseases in Helsinki Finland specially trained s c Allergy nurses keep track of the development of the general allergen situation of the country Through personal contact with the patients in the hospital correspondence with them and visits to their homes after discharge from the hospital as well as through contact with Public Health nurses and doctors throughout the country the Allergy nurses are able to provide a special home and family education of great importance This is supplemented with written pamphlets and meetings of patients and their family members at which further educational programs are developed

DISCUSSION

B STOKVIS AND A J WELMAN

It is evident both from the literature and from our own experiences that a large number of patients with psychosomatic affections passed their youth in disharmonious families This circumstance is of consequential importance for the treatment of patients with bronchial asthma for which reason we shall briefly examine the factor family relationships

A family may be regarded as a structure of mutual relations among several persons living together We may consider the family as a psychological unit in which therefore no component elements should be studied separately The affective interaction between the members of the family is to a large extant determined by the family bond A closer study of this family bond enables one to differentiate between a normal and an abnormal family

The emotional relationship between different individuals may be based either on an *attachment* or on a *binding* relationship The mentally healthy person feels bound to his fellows he is able to meet the other person by a surrender of self he is capable of giving love The neurotic family on the contrary is characterised by a relationship based on *attachment* An individual who owing to disturbances in his mental development (e g through wrong education) has remained stuck in this attachment relationship with his milieu will retain an infantile erotic attachment to it He is capable only of feelings of dependence and can only receive love For a child attachment is the normal emotional relationship When adults are incapable of forming a bond with others and relations based on dependence remain prominent the family life is pathological These feelings of dependence obstruct the individual development of the members of the family This applies especially to the child which being still in the process of development has a strong tendency to identification Owing to the pathological family relations this tendency towards identification continues to exist right into adult life

Within the family the members exercise a mutually educative—and/or re educative influence on one another The family as educative milieu depends inter alia on

1) The personality structure of the members (temperament!)
2) The mutual relation between the parents (unconscious drives)
3) The parents sence of responsibility towards the children

As regards the latter point (3) the so-called *loving care* with which some devoted parents burden their children is often nothing more than the expression of a selfish narcissistic disposition Such parents abuse the child s dependence relationship with them In many cases the parents themselves have remained stuck in their own infantile erotic feelings of attachment they are incapable of giving love either to each other or to their children and strive only after the satisfaction of their own desires To this end they utilize the child with the consequences that may be expected

From the psycho-hygienic viewpoint the most important cause of a disturbed family life must be sought in the parents Since it is completely impossible to prevent neurotics from getting married disturbances in family will always tend to occur They are in fact the more likely because (in accordance with the geno tropic theory of Szondi) there appears to exist a strongly attractive force between neurotic individuals

The question may now be asked to what extent a disturbed family bond may also manifest itself in a psychosomatic affect on With regard to bronchial asthma Alexander already pointed to the occurrence of frustrations during infancy From the biographic anamneses of patients with bronchial asthma examined in the Leyden Psychosomatic Centre it appears that nearly 80 per cent had had a disturbed family relationship The psycho-diagnostic examination of these patients showed that they are neurotically aff cted This surely must lead to any family which they may eventually found also becoming neurotic

The attacks of bronchial asthma therefore might also be regarded as mani festations of a disturbed family life This naturally entails the consequence that the treatment of these patients should also involve the other members of the family

Illness is man s reaction to his milieu in order to create a pseudo-equilibrium To restore the original equilibrium it is necessary to tackle both the sick person and his milieu This in fact is the fundamental principle of the methods applied at the Leyden Centre either by psychotherapy or in case work

CHOICE AND CHANGE OF PROFESSION

by

D A WILLIAMS

The choice of a profession depends essentially on the individual on his or her educational ability and interest which is dependant on intelligence personal drive and steadiness health family background and on opportunity Our aim for the asthmatic is to recommend an attainable occupation which will give a reasonable standard of health and happiness and where there is no increased hazard

Occupational guidance as has been pointed out by Schwartz (1953) is of special importance to the asthmatic as occupational asthma often starts at an age in which it is usually an economic disaster to effect a change He states that a survey of the occupations in which asthma is particularly disabling would be of the utmost value

Table I shows a list of occupations or groups of occupations arranged in increasing prevalence of incapacity due to asthma their sizes in thousands their certified spells of incapacity in thousands the spells of incapacity per hundred for each occupational group and at the bottom of the list the average for all occupations By spells of in capacity is meant a period of absence from work for more than four days The mean duration for asthma was in fact fifteen days The figures relate to males and with certain exceptions cover the working population the employed and self-employed (plus those who have lapsed from employment) *

The figures have been obtained from the Ministry of Pensions and National Insurance (Digest of Statistics Analysing Certificates of Incapacity, 1951—1952) The upper eight occupations are all occupations where the amount of incapacity caused by asthma was less than the average and can therefore be considered suitable The ten occupations below the line all have amounts of incapacity more than the average and are therefore unsuitable

On looking at those listed occupations one may wonder if some occupations owe their positions to their having been avoided and whether others may be over weighted by asthmatics having selected or drifted into them It is a possible fallacy, but to what extent this occurs we have no means of estimating in all probability it is insignificant or at the most very slight

* Groups excluded mariners while at sea members of the armed forces and non industrial civil servants

TABLE I

Occupations listed in order of increasing prevalence of spells of incapacity
Asthma males (1951) Great Britain

Occupations	Population at risk in thousands	Spells of Incapacity in thousands	Spells of Incapacity per cent
1 Administrators directors managers	373	0	—
2 Professional & technical	695	1	144
3 Commerce finance & insurance	1 328	2	151
4 Agriculture horticulture & forestry	1 052	2	190
5 Engineering metal manufacture	2 521	5	198
6 Workers in wood cane cork	484	1	207
7 Persons engaged in personal service hotels clubs institutions	491	1	204
8 Workers in building & contracting	902	2	222
9 Fitters machine erectors	813	2	246
10 Clerks typists	793	2	252
11 Road transport workers	788	2	254
12 Warehousemen storekeepers packers	363	1	275
13 Electricians electrical apparatus makers & fitters	358	1	279
14 Painters & decorators	332	1	301
15 Railway transport workers	316	1	316
16 Water air & other workers in transport & communications	293	1	341
17 Workers in unskilled occupations	1 233	5	406
18 Coal Miners	630	3	476
All Occupations	14 400	35	243

Information obtained from the Ministry of Pensions & National Insurance Digest of Statistics Analysing Certificates of Incapacity 1951—1952

Calculations checked by E Lewis Faning D Sc Ph D F S S Department of Medical Statistics Institute of Preventive Medicine Welsh National School of Medicine

Another possible error is that some workers may tend to go off sick more readily than others Some engaged in work entailing only slight physical exertion may continue at work while others engaged in heavy physical work may go off sick with the same degree of illness, financial considerations may also have their effect These considerations again appear to be relatively unimportant for a person who is able to continue work in a relatively sheltered and economically satisfactory occupation is obviously better off than one who is not

A third possible fallacy might be if the age grouping in these occupations varied very considerably for there is appreciably more incapacity from asthma over the age of fifty years than under fifty years

Table II shows a comparison of asthma and the infective conditions bronchitis nasopharyngitis (the common cold) and influenza For asthma the positions of the occupations are shown as before for bronchitis nasopharyngitis and influenza the position of each occupation and its percentage spells of incapacity is shown The percentage for the total population in each illness is shown at the bottom of the respective columns

Let us take the top eight occupations first There is a large measure of agreement here Before only three figures can we see plus signs Workers in building and contracting have a plus thirteen placing in bronchitis the percentage spells of incapacity being just above the average 3 55 per cent as against 3 30 per cent This amount above the average is hardly significant Workers in engineering have a plus eleven placing in the common cold but here again the amount of incapacity 1 309 per cent as against 1 306 per cent is not significant Workers in wood have a plus ten placing for influenza with incapacity again only very slightly above the average 8 0 per cent as against 7 8 per cent We can see therefore that those occupations with less incapacity from asthma than the average have with the slight exceptions mentioned less incapacity from bronchitis nasopharyngitis and influenza than the average

In the ten occupations below the line there is again much general agreement between incapacity from asthma and from these infective conditions Electricians and painters and decorators are however outstanding exceptions In both these groups of occupations their thirteenth and fourteenth positions in asthma are not in the least in agreement with their relatively high placings in these infective illnesses

Except therefore for these two outstanding exceptions it would indeed appear that the tendency to nasorespiratory infection plays a definite part in the suitability or otherwise of an occupation for an asthmatic

Comparison of asthma & bronchitis nasopharyngitis (common cold) influen a by percentage spells of incapacity per occupational group
Males (1951) Great Britain

Occupations	Asthma	Bronchitis		Nasopharyngitis		Influenza	
	Position	Position	/ Spells of incapacity	Position	/ Spells of incapacity	Position	/ Spells of incapacity
Administrators directors managers	— 1	— 1	536	— 1	268	— 1	1 6
Professional & technical	— 2	— 2	1 29	— 5	863	— 6	6 8
Commerce finance insurance	— 3	— 4	1 58	— 3	527	— 2	5 1
Agriculture horticulture forestry	— 4	— 3	1 42	— 2	475	— 4	5 5
Engineering metal manufacture	— 5	—11	3 21	+11	1 309	— 9	7 7
Workers in wood cane & cork	— 6	— 7	2 69	— 9	1 240	+10	8 0
Workers engaged in personal service (hotels clubs institutions)	— 7	— 6	2 65	— 4	611	— 2	5 1
Building & contracting	— 8	+13	3 55	— 7	1 109	— 7	7 1
Fitters machine erectors	+ 9	—10	3 20	+15	1 599	+15	8 7
Clerks typists	+10	— 9	2 90	+13	1 39	+14	8 4
Road transport	+11	12	3 30	—10	1 269	+13	8 3
Warehousemen storekeepers	+12	+14	3 86	+17	1 653	+10	8 0
Electricians	+13	— 6	2 23	— 8	1 117	— 8	7 5
Painters & decorators	+14	— 8	2 71	— 6	904	— 5	6 0
Railway transport	+15	+15	4 11	+14	1 582	+17	10 1
Water air & other transport	+16	+16	5 12	+12	1 365	+12	8 2
Unskilled	+17	+17	5 92	+16	1 622	+16	8 8
Coal Miners	+18	+18	8 1	+18	5 556	+18	18 0
Average spells of incapacity			3 30		1 306		7 8

— Indicates that the incapacity is less than the average for all occupations + Indicates that the incapacity is greater than the average for all occupations

Information based on figures obtained from the Ministry of Pensions & National Insurance Digest of Statistics Analysing Certificates of Incapacity 1951—1952 Calculations checked by Dr E Lewis Faning D Sc Ph D F S S Department of Medical Statistics Institute of Preventive Medicine Welsh National School of Medicine Cardiff

Table III compares the position in asthma with the positions and spells of incapacity expressed as a percentage of each occupation in nervous debility and in psychoneuroses and psychoses that is with illnesses due to nervous upsets (I am sorry that the figures for psychoneuroses and psychoses were not split up) Let us take the top eight occupations first All these occupations have position in these illnesses which are better than the average

In the lower ten occupations again except for electricians and painters and decorators there is general agreement between illnesses due to stress and asthma

Table IV lists all the illnesses we have been discussing in order of increasing incapacity

The comparison of these figures is not without interest Administrators directors and managers have the least incapacity in asthma in the infective respiratory groups and in the psychological groups

The terms administrators and directors need no explanation but the term manager needs a little amplification In the main managers include all those in executive positions drawn from all occupations including industrial occupations such as mining chemical engineering and building etc i e when they cease to work in these occupations as such and take up office work In this group are the financially and socially successful It would appear that financial success must play a large part in the prognosis of asthma Responsibility success good food, good homes with low physical demands have no ill effect on asthma, in fact these appear to be the most desirable attainments for the asthmatic

Professional and technical occupations are also eminently satisfactory for asthmatics These occupations include the recognized professions, the Church Law Medicine as well as medical auxiliaries teachers, professional engineers surveyors architects statisticians and mathematicians authors editors journalists and officials of political industrial and trade associations As with the previous group these occupations are in the main in the upper social classes

Commerce finance and insurance again a satisfactory group of occupations on all counts

Commerce includes commercial travellers proprietors of commercial concerns and their salesmen and their shop and other assistants i e those working in the wholesale and retail businesses e g grocery green grocery meat fish poultry confectionery and miscellaneous stores Finance includes company directors bankers stock brokers auctioneers and estate agents Insurance includes insurance managers underwriters brokers agents and canvassers

Agriculture horticulture and forestry is among the most suitable occupations for asthma and all the other diseases listed This group

TABLE III

Comparison of asthma & nervous debility psychoneuroses & psychoses by spells of incapacity

Asthma males (1951) *Great Britain*

Occupations	Asthma	Nervous Debility		Psychoneuroses & Psychoses	
	Position	Position	/ Spells of incapacity	Position	/ Spells of incapacity
Administrators directors managers	1	— 1	—	— 1	268
Professional & technical	2	— 8	288	— 5	432
Commerce finance insurance	3	— 5	226	— 3	377
Agriculture horticulture forestry	4	— 2	095	— 2	285
Engineering metal manufacture	5	—13	357	— 7	555
Workers in wood cane & cork	6	— 4	207	— 4	413
Workers in personal service (hotels clubs institutions)	7	— 3	204	—10	611
Building & contracting	8	—11	332	— 6	554
Fitters machine erectors	9	+14	369	+13	738
Clerks typists	10	+15	378	+15	883
Road transport	11	+16	381	—12	635
Warehousemen store keepers	12	— 6	275	+14	826
Electricians	13	— 7	279	— 8	559
Painters & decorators	14	— 9	301	— 9	602
Railway transport	15	—10	316	—11	633
Water air & other transport	16	—12	341	+17	1 024
Unskilled workers	17	+17	649	+16	973
Coal Miners	18	+18	1 11	+18	1 43
Average spells of incapacity			361		660

— Indicates that the incapacity is less than the average for all occupations
+ Indicates that the incapacity is greater than the average for all occupations

Information based on figures obtained from the Ministry of Pensions & National Insurance Digest of Statistics Analysing Certificates of Incapacity 1951—1952 Calculations checked by E Lewis Faning D Sc Ph D F S S Department of Medical Statistics Institute of Preventive Medicine Welsh National School of Medicine Cardiff

TABLE IV

Asthma bronchitis colds influen a nervous debility psychoneuroses & psychoses
Asthma males (1951) Great Britain Table listing positions of occupations

Occupations	Asthma	Bronchitis	Colds	Influenza	Nervous Debility	Psychoneu roses & psychoses
Administrators directors managers	— 1	— 1	— 1	— 1	— 1	— 1
Professional & technical	— 2	— 2	— 5	— 6	— 8	— 5
Commerce finance insurance	— 3	— 4	— 3	— 2	— 5	— 3
Agriculture horticulture forestry	— 4	— 3	— 2	— 4	— 2	— 2
Engineering metal manufacture	— 5	—11	+11	— 9	—13	— 7
Workers in wood cane & cork	— 6	— 7	— 9	+10	— 4	— 4
Workers in personal services (hotels clubs institutions)	— 7	— 6	— 4	— 2	— 3	—10
Building & contracting	— 8	+13	— 7	— 7	—11	— 6
Fitters machine erectors	+ 9	—10	—15	+15	+14	+13
Clerks typists	+10	— 9	+13	+14	+15	+15
Road transport	+11	12	—10	+13	+16	—12
Warehousemen storekeepers	+12	+14	+17	+10	— 6	+14
Electricians	+13	— 6	— 8	— 8	— 7	— 8
Painters & decorators	+14	— 8	— 6	— 5	— 9	— 9
Railway transport	+15	+15	+14	+17	—10	—11
Water air & other transport	+16	+16	+12	+12	—12	+17
Unskilled	+17	+17	+16	+16	+17	+16
Coal Miners	+18	+18	+18	+18	+18	+18

— Indicates that the incapacity is less than the average for all occupations

\+ Indicates that the incapacity is greater than the average for all occupations

Information based on figures obtained from the Ministry of Pen ions & National Insurance Digest of Stati tics Analysing Certificates of Incapacity 1951—1952 Calculations checked by E Lewis Faning D Sc Ph D F S S Department of Medical Statistics Inst tute of Preventive Medicine W l h N tion l School of M di ine Ca d ff

includes farmers gardeners forestry and horticultural workers and those with ancillary occupations to agriculture Their increased exposure to extrinsic allergens such as pollen and mould spores and in some cases animal danders does not appear to affect them appreciably as a group as regards incapacity One wonders if asthmatics do tend to avoid these occupations These figures show no reason for avoiding agri culture but on the contrary suggest that asthmatics might be encouraged to take up agriculture

The next group engineering and workers in metal comprises a very wide and large group varying from furnacemen foundry workers smiths metal workers of various types to scientific instrument makers and workers in precious metals Although the spells of incapacity for asthma in this group is satisfactory this group has a higher tendency to infections and a slightly higher tendency to nervous upsets than the position occupied in asthma would warrant As a group this has a satisfactory placing in asthma but one might well consider what branch or sub group the asthmatic is advised to take so that the tendency to infection would be less than the average for the group nor should the psychological suitability the economic return of the work and the chances of promotion to the administrative or managerial positions be ignored

Workers in wood cane and cork comprise a comparatively small group In general it is a fairly satisfactory group and its position in this list is perhaps not surprising

Personal service i e workers in homes (domestic of all types) in hotels restaurants clubs and institutions and includes hair dressers photographers and laundry workers—all who give a personal service Again a fairly satisfactory group of occupations for asthmatics having a higher position than perhaps we as allergists might have suspected

Building and contracting needs little explanation As the prevalence of bronchitis in this group is higher than normal asthmatics in this group should take extra care to avoid respiratory infections

Fitters machine erectors includes tool makers and fitters fitter assemblers maintenance engineers motor mechanics and other machine erectors and fitters You will notice the marked tendency to influenza and the relatively high rate of nervous upsets

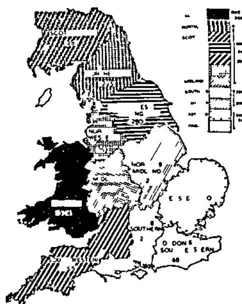
Clerks and typists This of course refers to men only and it sur prised me that it was so low in the list It includes costing estimating and accountancy clerks secretaries but not company secretaries and office machine operators Essentially they work in an office the same as administrators managers and directors except that they rarely have an office to themselves and their economic position is obviously much lower Their tendency to upper respiratory infection is comparatively

high as is their tendency to nervous manifestations Their comparatively low position in our asthma list is probably associated more with their economic state than with their actual working conditions One might have wondered if some asthmatics might not have drifted into these occupations but the evidence would appear against it

Road transport eleventh causes less debility from asthma than does railway transport or water and air transport presumably due to the fact that they are in their lorries have less physical exertion and less direct exposure to the elements

INFORMATION OBTAINED FROM MINISTRY OF PENSIONS & NATIONAL NSURANCE DIGEST OF STATISTICS ANALYSING CERTIFICATES OF INCAPAC TY 1951 1952

PERCENTAGE OF SPELLS OF INCAPACITY CAUSED BY ASTHMA



Warehousemen storekeepers packers of furniture china and glass and bottlers Here again is an unsatisfactory group of occupations and their position on the list of asthma fits in with the other illnesses There is a very high incidence of the common cold in this group Here again one wonders whether people who have become or originally were somewhat incapacitated have been attracted to this type of work but the correlation of incapacity between asthma infection and stress in the group is against this

Electricians and painters and decorators It is of special interest

that in the infective and stress illnesses they have a consistently and considerably higher placing than in asthma Many painters and decorators and some electricians are undoubtedly excessively exposed to that very potent allergen house dust Fumes from paints and non specific dusts in both occupations may also play a part Economically they are about average The other alternative is that many asthmatics have chosen these occupations but this appears unlikely Whatever the reason we must consider these occupations unsuitable for asthmatics

The last two groups are obviously the worst not only for asthma but for the other illnesses listed The figures here are quite consistent Economically the wages in coal mining are relatively good and their position as the worst occupation is probably entirely due to their work

I would however draw your attention especially to the lowly position of the unskilled workers I have for many years urged asthmatic children to work hard at school to develop mental capabilities to compensate for their physical disabilities In asthmatics at work I urge them to be conscientious and thorough to develop steadiness and personal drive so that they do not change their occupations frequently and so end up in this group of unskilled workers

Finally the map shows that in Britain the place of occupation for males also significantly affects incapacity from asthma It shows that there is less incapacity from asthma in the South East districts of Britain (the warmer and drier parts) than in the western and northern districts (the wetter and colder parts) Therefore in choice or change of occupation the locality should also be considered This latter consideration may be especially considered in the middle aged asthmatic where a change of locality may be more easily brought about than a change of occupation or profession

In summary I would suggest that in the choice or change of profession we should consider 1 the resulting economic position 2 the liability to naso respiratory infection 3 the liability to stress and last but not unimportant 4 the liability to extrinsic allergens as well as the locality

It is with pleasure that I acknowledge my indebtedness to Dr Lewis Faning D Sc Ph D Department of Medical Statistics Institute of Preventive Medicine Welsh National School of Medicine Cardiff for his help and advice with the figures presented

Reference

SCHWARTZ M (1952) *A ta all golog ca V* Supplement II

flour allergy leading step by step from a rhinitis over bronchial asthma to an emphysema However the workers in the spinning mills will usually not live to this late stage of the disease since they will become transferred after their first asthmatic episodes (although even then too late) into rooms clear of sericin dyeries packing rooms etc

Every worker ought to be examined as much as every miller and baker every 3 or 6 months for the symptoms of sensitization (skin reactions or other manifestations) If positive findings exist the person affected should be withdrawn from this type of work and if feasible be given another occupation

3) Exposure to dust of *castor beans* This is a very active allergen causing severe allergic reactions even in minute concentrations Sensitization takes readily place the preparatory period is only short provided that there is a *close* contact Epidemic asthma occurs in the vicinity of factories in which castor beans are processed while their dust is expelled into the open air However the disease will not become evident among persons who recently moved in the surroundings of the factory but only among those that lived there for a certain length of time This span represents the sensitization period Sensitization will not occur unless the dwelling lies within the reach of the gaseous by products with their allergen bearing dust particles Thus the epidemic originates by means of temporary exposure to the allergen —comparable to the spreading of an epidemic of typhoid by the dissemination of the typhoid bacillus through contaminated water milk or the like I myself[1] have examined such cases and more asthmatic epidemics owing to the dust of castor beans have been described in U S A bei Figley and Elrod [2] Zerbst[3] and a new by A U Cintra und E Mendes [4] Important are the corresponding experiments by Ratner and Gruehl [5]

4) The same principle of pathogenesis is also realised in Printer s asthma (Hoschek [6] Fowler[7]) although the allergen is a different one it is represented in the gum arabic *resin* used as powder in the process of wet spraying The symptoms of this disease gradually develop in the same manner as in the 1st and 2nd example

5) Mention is also made of the asthma arising in factories producing *mother of pearl buttons* Here the principle works according to the allergy to oyster shells described by W Gronemeyer[8] detailed description hereof is given on the First International Congress for Allergy Zurich (see fig 2 and 3)

6) *There exist some more observations on this subject which will not be considered* here as I am presenting only own contributions or some few clear cut communi

[1] *Hefte zur Unfallheilkunde 44* (1952) S 221
[2] *J A.M A 90* (1928) 79
Industr Med 13 (1944) 552
[4] *J Allergy 25* (1954) 253
[5] *Am J Hyg 10* (1929) 236
[6] *Polygraph 1953* S 611 (Heft 20)
[7] a) *Lancet 16* (195.) 755 b) Intern Arch. Allergy etc 6 (1955) 1.0
[8] *1st Intern Cg Allergy* 1951 Proceedings p 285



Fig 1

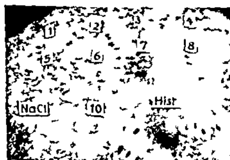


Fig 2

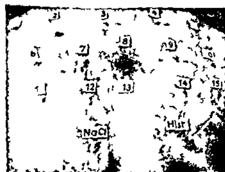


Fig 3

cations to the problem as given in the scientific works of Royle[1] Wyers[2] and others asthma from dust derived from cotton seed sheep s wool coco nut fibre etc

All these observations stress the significance of the *invasion by some allergen* for the pathogenesis of bronchial asthma Whatever gets registered as bronchial asthma either in our clinics or in general practice is based on the same principles Unfortunately there are so many cases of allergy with a long history the clinical symptoms of which became overflowing only now or went unnoticed for years although fragments of the process existed long before Every year the number of allergic persons augments among which the analysis of some antigen is success fully performed demonstrating a specific cause of the disease Yet these analyses generally are carried out too late The fragments and the complete syndrom of the disease will as an old habit be referred to as *infectious* although specific allergens recently have become demonstrated more and more But an old doctrine postulates the infection as the basis of all inflammatory reactions the carriers of which formerly were said to be the bacteria which now are completed by the virus Although the conception of a hyperergic inflammation due to allergens is wide-spread its correct use is not too frequently encountered Thus the old theories of an infectious etiology still retain general esteem This fact also often leads to a misplaced anti infectious therapy (Penicillin etc) However there exists occasionally a preparation and introduction of the allergen invasion by a common infection but this only serves as an accessory condition for the formation of an allergy I am not discussing these relations in detail here It must be stressed that the occupational asthma represents an ideal example of the pathogenesis of bronchial asthma and that it is the *allergen* which is to be placed in the focus of pathogenesis irrespective of other conditions that favour the disease ranging from psyche to climate

It is not practicable in every case to prove this thesis by demonstrating the allergen. However the more skilful and exact the patient s history is elaborated the investigations done the surroundings observed the richer the findings will be *Every case cleared* supports the principle *Statistics* can barely be that con vincing because of the complex correlation of internal and external additional factors of the disease—with the exception of the occupational asthmatics these permit a clear recognition of a common allergen the abolition of which can success fully be achieved This abolition is immediately effective but must be performed soon after the first onset of the disease During this stage recovery of the irritated mucous membranes and restitution of normal breathing can still easily be attained

Only in case of an *inveterated asthma* the situation is much different secondary lesions of the mucous membranes as metaplasia of the epithelium chronic bronchitis derangements of innervation (pathological chain reactions fixed conditioned reflexes) harder organic lesions such as emphysema and bronchiectasis are irreparable Tissues of low functional value as scar tissue have then replaced the normal tissue with its regular function

For these *heavily* damaged asthmatics symptomatic therapy granted by drugs

[1] *1st Int rn Cgr Allergy* 1951 Proceedings p 76

[2] *I te n Arch Allergy* 6 (1955) 119

gymnastics psychotherapy changing of environment and climat means a certain but not entirely satisfactory relief

If the described connections would become generally acknowledged the importance of the patient s history recognized and the gradual development of the disease comprehended then the first symptoms could be traced back to a (possible) allergy An analysis of the allergens could be achieved and on the basis of protection from the allergen further damage—particularly the incurable final stages of the disease—might be readily prevented

INHALATION RISKS OF FUNGAL SPORES TO BUILDERS AND DECORATORS

by

K MAUNSELL

Since a high percentage of patients suffering from bronchial asthma with house dust and fungus allergies was found among builders and decorators quantitative estimation of the concentration of airborne spores was carried out in 2 London houses under structural repair and compared with 6 normal dwellings (slit sampler) Sampling was carried out in a room adjacent to the one in which the builders were working The rooms had no direct communication but led to a common hall A tenfold increase was noted in the total spore count inside dwellings when building was in progress The increase was mainly due to Penicillium It must be assumed that the concentration of airborne spores in the room in which the men were actually at work was considerably higher and that prolonged exposure to such air may well lead to asthma in allergic builders and decorators

Reference

MAUNSELL K (1954) *Internat Arch of Allergy and Appld Immun 5* 373

B STOKVIS

The experiences in our Leyden Psychosomatic Center proved that in several cases difficulties and frustrations in the profession are of more importance than those *in sexualibus* which are often considered as the most important psychic determinants in patients with asthma We always try to combine our psychotherapeutic measures with the case work of our (female) social worker The latter visits the employers and tries to improve the social situation and environmental factors in close co-operation with the psychotherapist

R S BRUCE PEARSON

In considering the figures that Dr Williams has shown us it is important not to over simplify their significance Although certain occupations may predispose to asthma it is also probable that certain occupations are more suitable for asthma

ties than others and these will therefore have a high incidence of asthmatics among them Many young asthmatics for example take up clerical work because they feel it will be within their capability Because there is a relatively high incidence of asthma among clerks it does not therefore necessarily mean that this occupation predisposes to the development of asthma

D A WILLIAMS

The natural history of asthma is to start in childhood to tend to disappear in the teens and in young adult life and to come back again in later life When we advise individual asthmatics in their choice of occupation we must obviously not advise an occupation where there is a big risk of allergic sensitization such as bakers printers etc and I would agree with this It is however important that we should take a very broad view of the choice of occupation for an asthmatic for in this way we can hope to prevent the return of asthma in later life in many cases asthma which so often leads to much incapacity

The miners in England and Wales are frequently x rayed and the incapacity listed as due to asthma could not be due to pneumoconiosis

CHILDREN S HOMES FOR ASTHMATICS*

by

SVEN KRAEPELIEN

Nowadays asthmatic children are a large part of the patients in our children s hospitals and in the offices of pediatricians As far as we can judge the number of asthmatic children has increased considerably during the last few decades even though we cannot get any exact figures In an investigation of the incidence of asthma in the Swedish schools I have calculated that the number of asthmatic children in our little country is about 10 000 In the elementary schools of Stockholm the incidence was about 1 4 per cent When the asthmatic children of pre school age are also taken into account—a very large group whose exact number cannot be definitely established—the serious pediatric and social problem of asthma becomes even more obvious Similar figures for frequency are to be found in Norway and in Holland

For technical and many times for psychological reasons asthmatic children are usually investigated at the hospital and the treatment is generally started there A frequent and regular control is always necessary which is upsetting for the child as well as for its parents Unfortunately it is often necessary to discharge children from the hospital at a time when for various reasons it is not convenient for them to return to their homes A satisfactory adjustment of the home environment from an allergic point of view is not always possible for instance because of the father s profession or unfavourable home conditions Small apartments with difficulties concerning good dust hygiene increase the risk of infections During the treatment period there should always be the possibility of placing this group of children for various lengths of time away from the family in a suitable home like a convalescent home It is true that asthmatic children can stay in ordinary convalescent homes together with other children but the character of their illness is always a hindrance to their being admitted to the home Often the personnel is afraid to handle the acute attacks of the asthmatic children Also the length of time the children are allowed to stay at these ordinary convalescent homes is limited by the lack of places there At least this is the case in Sweden and I suppose this is also true in many other countries For asthmatic children a two or three weeks stay away from their home environment is not sufficient often they

From the Pediatric Clinic of Karolinska Sjukhuset Stockholm (Head Professor A Wallgren)

often become quite free from symptoms as soon as they come to the hospital without any therapeutic measures at all A hygienic environment from an allergic as well as a psychological point of view is the probable explanation Since 1936 a boarding school for about 20 asthmatic children has existed in Stockholm The home is situated in Stockholm itself and is only a few metres above the sea First the equipment of the home has aimed at a rational dust hygiene The children live there during the school terms and usually get leave of absence every weekend In the summer when most asthmatic children have their best period —except those sensitive to pollen—the children usually stay at home or at public summer homes together with other children The shortest time of attendance has been one term and the longest 14 terms During the first days after their arrival at the home most of the children have become free from their asthma attacks All have been able to complete their school attendance interrupted of course by intermittent illnesses, but less often by asthma attacks During their stay at the asthma home all the children have received aspecific desensitizations with colloid sulfur, sometimes combined with bacterial vaccines therapy In a follow up study with an average observation time of 3—4 years it is seen that about 90 per cent of the children from the asthma home have become free from attacks that had badly influenced their condition or occupation The good results from the asthma home in Stockholm are quite as good as those from mountain asthma homes even though the published results cannot be compared in all respects

As not all countries have the desired topography for such homes in the mountains I want to stress as my personal opinion that it is not necessary for such homes to be at higher altitudes far away from home environments and above all quite inconvenient

With the high incidence of asthma in children today in most countries it is desirable that a sufficient number of suitable institutions is established so that more children who need such care may have this advantage In Sweden the interest in this matter has had good results during the last few years In the spring of 1955 the Swedish Red Cross started another school home for asthmatic children and in several Swedish provinces they are preparing similar institutions

What are the requirements for an asthma home? An asthma home should be centrally located in the neighbourhood of a big town or in the center of a province As climatologic factors have hardly any decisive importance for the asthmatic children there is no reason to place the home in high altitudes which often means transportation for longer distances and thus more inconveniences A good reason for a central position of an asthma home is first the need for close contact with pediatric hospitals As the child with acute attacks should have the

possibility of immediate hospitalization the relative proximity to a hospital must be the decisive factor in its location The parents must have the security of knowing that their child will be able to get help and adequate attendance when having an asthma attack Another important reason for the central location of an asthma home in a town or a province is that the parents will be able to visit the child rather frequently This is specially important for the preschool child as a long separation from home and parents may have a detrimental effect on the child s health in the long run an extremely important circumstance only recently given the proper consideration The parents thus have frequent assurances of the child s welfare and may observe with their own eyes in what environment he is living

In every asthma home it should be possible for the children of school age to attend classes Classes can of course be held in the home itself but as a rule such arrangements make the costs higher It is less expensive and often quite sufficient if the children can have their education at a nearby school In a large city where there are more extensive educational facilities and better possibilities for collaboration with school authorities this problem of co operation between school and home can be solved practically so that more or less irregular pupils may continue their studies

The duration of the asthmatic child s stay at the home should not be fixed in advance but should be determined by the individuals need The time of attendance should not be shorter than 3 months that being the shortest period with any therapeutic importance

A further requirement for an asthma home is that there must be a specialized nursing personnel Even at the home the children should be able to get the help they need for their attacks To avoid any insecurity in their minds the parents must be convinced that there is a competent personnel at hand If there is not a competent staff one can very well understand the parents hesitancy in sending their children to the home The parents know more than anybody else that their child needs special care The home should be under the guidance of a physician preferably a pediatrician

In spite of the inconveniences that separation of children and parents may bring about the many good results we observe when taking asthmatic children from their home surroundings for varying lengths of time suggest that we always should have available the facilities to do so whenever indicated Even if the stay in special asthma homes —whether mountain or city—does not bring about more constant results it often gives the children an interval in which they feel better and more like other children Their physical and psychological condition

often improves and may facilitate the continued therapy in their own home environment

SUMMARY

With respect to the high incidence of asthma in children the author discusses the need of special homes for asthmatic children and the importance of a change of environment for some of these children as a necessary part of the therapy The placing of asthma homes at high altitudes in the country as opposed to the more convenient city locations is discussed The author himself prefers the last mentioned alternative and presents his reasons

THE INSTITUTIONAL REHABILITATION OF THE INTRACTABLE ASTHMATIC CHILD

by

H S TUFT

Fifteen years ago a definitive program for the institutional rehabilitation of the intractable asthmatic child was started at the Jewish National Home for Asthmatic Children Denver Colorado This program was conceived by Dr M Murray Peshkin [1] who in 1930 expressed the need for such an institution In the course of this operation certain concepts of the development of intractable asthma have been recognized There has been also an attempt to define the reasons for the obvious results inherent in this procedure This paper will attempt to cover both phases so as to provide a basis for further discussion in this field

In the early days of this program it became apparent that separation from the home environment was effective in controlling asthma in approximately forty two per cent of the children admitted to the institution These children would have no further asthma during their stay which usually was a two year period A second group comprising forty per cent of those admitted showed progressive lessening of severity and frequency of symptoms in the first year of residence and complete loss of symptoms in the second year The remaining 18 per cent of the children were either not helped at all or learned only to tolerate the symptoms already present

The immediate cessation of symptoms upon arrival at the Home in the group so affected gave rise to speculation concerning the reason for this result A theory of the development of intractable asthma was developed which included the following factors heredity allergy infection and finally the emotional overload It would be redundant to cover the first three factors but the fourth factor needs a great deal of clarification

By the term emotional overload is meant the additional burden carried by an asthmatic child in a disturbed unhappy or tense home environment *It has been postulated that such a burden may be the one* single factor which converts an ordinary asthmatic child into one who will not respond to conventional anti allergic therapy It has been further postulated that the emotional environment may actually cause a break down of the immune mechanism There is the probability that ten per cent of asthmatic children fall into the category of intractable asthma One should not however conclude from the foregoing that

the lessons learned in the intractable asthmatic necessarily need apply to all asthmatic children

It is our feeling that the type of emotional overload which most of these children manifest is described quite completely by Abramson s concept of the Cronus complex Although the theory of maternal rejection as proposed by Miller an Baruch [3] has been widely circulated we cannot see the application in our patients at the Home We believe that maternal rejection is part of our twentieth century culture and is common in all child parent relationships We feel that there is no greater incidence of this symptomatology in the asthmatic child and further that this symptom is not responsible for the production of the intractable state

Certain technical matters should be discussed at this point in order to clarify the matters of admission procedure and the discussion of the application of treatment technics The age of children to be admitted is restricted to those five years of age up to and including 16 years Younger children have not been admitted because of the tremendous cost of the custodial problems involved Older patients cannot be admitted because the physical plant does not allow for adequate supervision of the older teen ager

The sole medical criterion for admission is the diagnosis of intractable asthma Intractable asthma is defined as severe perennial asthma requiring frequent hospitalization which continues despite adequate sustained therapy including complete allergic workup

To make maximum use of treatment in the institution a sick child must be ready to separate from the family The child must have the capacity to live in a group situation The IQ must be in the normal range for those with subnormal IQ ratings cannot make maximum use of psychiatric casework The family must be able to allow separation and must be willing to continue in a casework relationship while the child is under care This study is made by the casework agency (family welfare child welfare or child guidance) in the hometown of the patient

The Home is located on a 17¼ acre tract in the heart of Denver Children reside in cottage type buildings with each child having an individual room or a cubicle Each cottage is supervised by a house father or a house mother usually in the number of one house parent to ten children The children attend public schools in the vicinity The grade school is located approximately four blocks from the Home the Junior High School is across the street from the Home and the High School is within walking distance of the Home The staff also includes a full time athletic director and part time recreation personnel

Four features of treatment and rehabilitation are recognized The simple matter of separation from the home environment is perhaps the

most important in the eventual rehabilitation It should be stressed that this in all probability represents a tremendous total environmental change which includes both freedom from contact with allergens as well as removal from emotional tension of the home The word parentec tomy has been coined by Doctor Peshkin to describe one feature of the separation This alone cannot account for the immediate result but may be responsible for some of the long term results

The matter of climatic change comes in for a great deal of discussion but there are many features of the weather in Denver that mimic to some extent those in home communities Generally speaking the Denver climate is drier there being many more days with humidity being less than 20 per cent However there are wide temperature swings from day to night and periods of precipitation and gale like winds which also are present in other areas of the country The altitude of Denver is 5280 feet above sea level but it must be stated that this has never presented any problem with regard to respiratory function

The next facet which is deemed of importance is the matter of group living It is now a well recognized fact that children afflicted with chronic disease do much better in an institution dedicated solely to that disease rather than in a general institution There is a great deal to be said for the ability to look at one s neighbour with similar afflictions without shame or reproach

Many children have been hospitalized frequently or have spent many hours in bed They have forgotten what it is like to play with other children Institutional living helps in this field as well as in the field of new adult experience and restoration of confidence House parents assigned to each group are educated in the physical and emotional aspects of asthma so as to view the child in a different perspective than his own parent The child reacts to this attitude with a calmer less harrassed feeling which aids his eventual rehabilitation Athletics arts and crafts and music training are other facets of the group living approach

It would not be in the scope of this paper to discuss allergy therapy in general Suffice it to say that the recognized technics of testing and treatment are utilized in the institution much in the same way as in the child s own area We have seen many instances of pollen therapy becoming effective during their residence at this institution whereas it was apparently ineffective previously

The success of the role of the psychiatric therapy in eventual re habilitation causes a great deal of comment from the profession Never theless one can point out that some type of psychiatric therapy is necessary in any child separated from his family and involved in an institutional setting The degree of psychiatric therapy depends upon

the problems presented It is our feeling that the highly trained social worker from an approved school of social work and having at least a master s degree in the field is capable of handling most of the problems connected with adjustment to the institution, and to the living situation However therapy which need go beyond this more or less superficial approach should be done by analytically trained psychiatrists Psychiatrists must however have special adaptation for the work of children and a very good orientation in the asthmatic individual s problems in order to become completely effective in such a setting

The members of the social service staff work with those in other departments to help the child make maximum use of placement in the Home This is accomplished primarily in three ways

1) The social service worker reviews the child s history and contributes his observations to the people who are working more closely with the child In this way each adult having contact with the child gains a more complete understanding of him This interchange of knowledge and impressions aids greatly in planning the future treatment of the child

2) The social service worker keeps the parents informed of the child s general adjustment through reports to the social agency These reports enable the agency to help alleviate the parents concern about the child and to help the parents in reaching a better understanding of their own problems

3) The social service worker holds regular interviews with the child These interviews compose the greatest and perhaps most important part of treatment The permissive setting of the office enables the child to express himself through talk and play The relief of emotional tension this therapy provides makes the child more responsive to other treatment enables him to adjust more readily to the institution and prepares him for his eventual return to his family

Space does not allow a more complete evaluation of the total result However in general it might be said that 85 per cent of the children in the program have maintained their gains for up to 12 years Followup studies should be available to the profession within the next two years in the form of a monograph by Doctor Peshkin which is presently being written

The indication realized from this 15 year experience is that more facilities must be available for children falling into this category Pending a greater knowledge as to the reason for the effect of separation rehabilitation of the intractable asthmatic child must be expanded to include those patients restricted from this approach by reason of financial responsibility of the parents One may foresee the need for institutions of this kind in each country of the world as well as in connection with the large cities of the United States

References

1 PESHKIN M M Asthma in Children IX The Role of Environment in the Treatment of a Selected Group of Cases a Plea for a Home as a Restorative Measure *Am J Dis Ch ld 38* 774 (April) 1930

2 ABRAMSON H A Evaluation of Maternal Rejection Theory in Allergy *Ann Allergy Vol 12* 129—140 (March—April) 1954

3 MILLER H BARUCH D W Psychosomatic Studies of Children with AllergicManifestations I Maternal Rejection A Study of 63 Cases *Psychosom Med 10* 275 (September—October) 1948

DISCUSSION

IS IT USEFUL TO MAINTAIN NURSING HOMES FOR CHILDREN?

by

N J M AARTS

A change of appreciation of the Nursing home for Children may be seen nowa days In the beginning mostly only badly nourished children were sent to a home for a while—normally 6 weeks—to rise their weight by good food and by dividing the day in activity and rest in good proportion Later on there came also special homes for a special group of children for instance with asthma

To day the badly nourished children are seldom seen The indication that comes more and more into the list of indications is nervosity It means that a child is not capable of living its normal everyday life as it should it is badly tempered does not eat does not grow does not behave itself in the normal way does not sleep or awakes several times during the night with fear is lightly in fluenced by misfortune etc Mostly the cause of this abnormality lies in the family

Is there any reason to treat these children in a home?

The cause—the incongruities of the family—cannot be cured by removing the child and forstering it during a period of several weeks in a nursing home Still I believe we can do much good by giving these children a time of psychical rest outside the family even when knowing that a return to there will be necessary

Until now I spoke about nervosity but the same is true for asthma because next to other factors a mighty psychical component is there Therefore apart from the fact that medical care is necessary in the normal nursing home and special medical care in an asthma center the most important thing we have to do is to give these children a mental training without letting them know it is a mental training We can give them a better adaptation to reality we can teach them how to behave themselves with other people in the first place of course with other children but also in their contact with grown up people These 6 weeks—often twice as much—are as important to the child as a holiday of some weeks is to a working man And beyond this holiday we can give them so much!

For that reason in the nursing home there must not be a system as in a military camp The child is mentally unable to accept all it does not understand We must try—according to its capacity to understand—to show and teach the child why it has to behave the way we tell them and not in any other way! We must observe the children during their games and make use of these games We must give them the sense of being personalities but also that this personality is directed and formed by the social status of the human being I do not mean we should try to teach the child sociology but we can educate it in a way it will understand

How is the state of the nursing homes at the moment in trying to bring these children in the right position for life? Are there some other treatments necessary?

We can of course give the children a good time for 6 or 12 weeks but after that they go home and it is possible that the time in the nursing home was too short especially if the child has not the power yet to make up its own mind and to decide where and how to stand against the troubles in its family

Therefore we must think—*more than we have done before—about the family* While the child is in the home and better already before we must ask the help of the social worker! At first this person must make a report of the family social structural etc This report must be sent also to the doctor of the nursing home—in that case he can talk it over with the directing nurse and as a result of this the report might be of some help in the treatment of the child Next the social worker must try to change the family situation in talking with the parents separately and together Often it will be no case for the social worker but more for the psychiatrist Thus there must be co operation between the family doctor and the social worker We must use the time the child is not at home! After leaving the nursing home there is another task for the social worker to help the child to become part of the family again without becoming a neurotic child and to help the parents to treat their child in a more normal way But also there is a necessity of keeping contact with the nursing home for two reasons

1) the nursing home can give—also afterwards— some good advice

2) it is of much interest to the nursing home to hear how the child is getting on because it can be a testing of the methods used and indicate a change of these methods if necessary

The nursing home itself must be as much as possible a normal home It must not be too splendid with too much of a home in a nursery tale It must not be too big a change for the children from the familyhouse into the nursing home and back again Give them the same things to play with that they know from home Do not let them sleep in a room with too many beds do not make a dor mitory—personally I like bedrooms for about 6 children And as it is a home let them have the feeling that when in trouble there is always someone to help them—like mother at home Do not let them play all day long what the nurse in charge likes to do but give them also some time to do as they like

In this way I believe all our nursing homes have reason to exist and we cannot miss them!

As a result the youth of to day will be the psychical stronger generation of to-morrow

J DUCHAINE

From a limited experience with an asthmatic children s home established at the Belgian Coast the author draws the following tentative conclusions

It is desirable that the Home should be constructed in view of its special purpose Attention should be directed to the facilities necessary for play in allergen free surroundings

Problems arising from adequate schooling should be considered as the children have to spend at least 6 months in the home before they can be sent back During

their stay adequate desensitizing treatment should be given and the child should only return in his family if control of environments in his own house has been fulfilled

Diagnostic elimination diets can be used in the home although they necessitate full co-operation from the staff and the hotel management This last point is some times difficult to attain

THERAPEUTIC VALUE OF ASTHMA HOMES

by

J E C SCHOOK

A certain percentage of the children with bronchial asthma is at home resistent against every form of treatment All therapeutic measures we take fail and we can t succeed at home in trying to get a reasonable situation

These are the children who in the first place are considered for an admission to an asthma home and with these children is such an admission which means a long separation of the child from his family mostly justified

Why is it possible to treat these children better in an asthma-centre than in their own homes?

Of course there are many advantages which are very clear In the houses specially fitted for these children we can make the conditions of life as favourable as possible This concerns as well the allergic factors as the psychological sides of asthma

I shall not go into this subject But there is still one thing I think is very important which I will mention in this connection and which shows in my opinion the value of the asthma-centre very obviously and that is the possibility for an exact observation of the patient and of his attacks of asthma By this observation it often becomes possible to find out which factors are important for his type of asthma and how we have to treat them

You all know how difficult it often is to get a clear history from the parents of the asthmatic child and to form a just notion of the different factors which take part in the influences on the attacks of the child

When we have the child under our constant observation we can note very exactly his attacks and all influences which may be important In this way it is often possible to get a better view on the patient and his sensibilities

Also for the judgment of the results of the treatment an exact observation can be very helpful

I will give you a single example

In consequence of the many different factors which are active at home (allergic and psychological) the attacks of asthma become often so severe and so frequent that it is not anymore possible to separate the different causes from each other

Only as we bring the child in a favourable situation and a big part of his asthma vanishes we keep that part of his asthma that is the most important one and that we can treat with the best chances of success

When we add to this treatment of the child a treatment of the milieu the child comes from and where he has to return when he is dismissed we have a good chance to reach a good result in the end

B STOKVIS

I completely agree with the contents of this very interesting paper Only I should like to remark that in our view it is not useful to treat children outside their own milieu We prefer to treat the children psychotherapeutically when they are in their family environment When it is necessary to give the children a psychotherapeutic treatment in children s homes we always combine the individual treatment with sociotherapeutical measures group psychotherapy play therapy in groups psychodrama and a Punch and Judy show

K WILKEN JENSEN

Fundamentally I believe that it is best to treat an asthmatic child in its usual surroundings and I consider the sojourn in a children home as an emergency arrangement In Denmark we can send our children to a home in Norway (in the height of about 800 m) exclusively meant for asthmatic children or to an ordinary convalescence children s home where the attending doctor is especially interested in asthma this home is lying in Denmark where we—as you may know—have no mountains of this altitude In both homes most of the children are free from attacks as long as they are there but most of them relapse afterwards some of them even have an attack in the train or on the boat on the way home In Switzerland I was told that asthmatic children were sent to the mountains but that the pediatricians were well aware that the symptoms recurred when the child came down again I am not convinced either that the duration of the stay in the home is of much importance if no other treatment is given I have seen children who have been in the home for a year without any result The advantage is that the child gets a holiday from its symptoms and during this time the hyposen sitization can go on generally without unwanted side effects so that the resistance of the child is more or less restored as well specifically as totally

THE TREATMENT OF BRONCHIAL ASTHMA IN HIGH ALTITUDE CLIMATE

by

H WISSLER

It is somewhat difficult to speak about the climatic treatment of bronchial asthma because, conscious or not the hearer suspects the speaker to talk propaganda I understand this attitude very well While for instance hyposensitisation or psychotherapy may be done at least theoretically everywhere climatotherapy is confined to certain places and therefore experience of it is limited to a relatively small number of physicians All I can do is to emphasize that the facts I am going to present to you have been collected as honestly as possible and according to the rules of medical science

The high altitude treatment of bronchial asthma is time honoured At the place where I live i e Davos at an altitude of 1500 m (5000 feet) asthmatic patients have been under medical care for about 70 years There is more than one family whose ancestors came to Davos 2 or 3 generations ago because of asthma and settled there If we compare the first report published in 1906 with our recent studies there is no striking difference The experiences have been the same over the last 50 years

According to general rules I will first mention the facts which are well established and then the more obscure sides of the problem

All observers agree that the majority of asthmatics are free from asthma as long as they are in the mountains That is especially true for children It is always amazing to hear that children have had very frequent attacks over many years at home and to see them at Davos being completely free from asthma from the first day onwards In a study we started some years ago we found that among 200 children 85 per cent were free from asthma while the remaining 15 per cent had only infrequent and minor attacks The 85 per cent actually had no attacks while slight wheezing which did not hinder normal activity was not recorded During the last years we have marked any sign of asthma even the slightest on our medical cards with red and even so there are many cases with no red marks at all For the last few months we have been trying to establish clinically inapparent bronchospasms by measuring the timed vital capacity (Tiffeneau Test) before and after an epinephrine spray It seems that this silent bronchospasm is not infrequent and is not much influenced by the climatotherapy Yet our experience is very limited The number of attacks depends very much on the type of cases

under observation During the last year for instance we had a higher incidence than before This was due to a group of English children My English friends had collected as a test group the worst asthma cases they could find It took several months to get them more or less free from asthma but after a year the result was quite satisfactory

It is unnecessary to explain to you what it means for an asthmatic child to be free from attacks The consequences are striking, on the physical as well as on the psychological side The weight increases muscles become stronger the children often depressed and anxious become lighthearted and more self confident On the other hand I must mention that I never have seen a chest deformity or a marked degree of emphysema disappear You may ask perhaps what treatment we give apart from low barometric pressure Very little We have breathing exercises done in the majority of cases I think that a prolonged siesta on the balcony is useful for most of the children Apart from that rest period the physical activity is normal In summer walks in the mountains are taken as often as possible and in winter the children go to the icerink every day Yet we noticed that one has to be careful with these major physical exercises as many children tire very easily As to the educational side the children live in groups of 12—15 under the care of a trained nurse and have regular schooling in rather small classes Psychotherapy in the strict sense is not used but we try to increase the childrens self-confidence wherever we can As to the length of the cure there are no definite rules and each case is to be considered individually In general short cures of 1 month or so are found to be of very little use We think that 6—12 months is generally a suitable length of time to stay

To summarize the observations during the stay in high altitude in almost every case there is a considerable improvement of the general condition in the majority of cases disappearence of the clinical symptoms of asthma and in a minority only reduction of severity and frequence of the attacks

The essential question now is what the results will be after the children return home The usual objection to high altitude treatment is that the results are transitory and that a month after return the child is in the same state as before The question has been examined several times and the results were of a striking uniformity So it will do if I mention a follow up study we performed in collaboration with the university childrens clinic at Zürich a couple of years ago covering two groups of about 100 children each the one being treated at Davos the other in an asthma home in the Engadin at 1800 m The observation period varied between 1 and 6 years after return We divided the results into 3 complete success complete failure and between them, considerable improvement in severity and frequence of attacks Doubtful improvement

was registred as failure In this way we found complete recovery in 20 per cent failure in 25 per cent and improvement in 55 per cent or roughly speaking one quarter full success one quarter failure and two quarters improvement For the purpose of the present report I have checked the results once more and tried to get news of the children that had left the sanatorium in the years 1949–53 The proportion was once more the same the exact figures being as follows out of the 61 cases we got answers from 12 (20 per cent) were full successes 14 (23 per cent) failures and 35 (57 per cent) improvements

We should like to be able to predict the result while the child is still with us Yet up to the present all attempts in that direction have been unsuccessful Our researches suggested that the failures were more frequent among children who had had eczema or among those with an allergic family history but the difference was not statistically significant It may be that more accurate lung function tests may give us a clue but I feel rather that the factors which determine the final result are on the emotional side

Having mentioned certain well established facts we have now to discuss the mechanism by which the high altitude climate acts That will not take us long because we know very little

First let me deal with the objection that taking asthmatic children away from home and bringing them wherever it may be can sometimes have a beneficial effect and that the so called climatotherapy is nothing more than a change of milieu I am quite aware of the possible influence of simply separating the patient from his family and especially from his mother Yet I have seen quite a few cases that had been brought to children s homes in the lowland without any succes but who were free from asthma at Davos Very interesting information on this problem could be drawn from an English home at Davos where a considerable number of asthmatic children were being treated Many of them had spent a long time at residential open air schools in England without success and were free from asthma at Davos under very similar living and educational conditions So we think that there must be an almost specific factor in the high altitude climate but unfortunately we do not know what it is The climatologic side is pretty clear thanks largely to the skilful and patient work that has been done at Davos for many years first by Dorno and then by Morikofer The characteristics of high altitude climate which term is generally applied to places over 1200–1500 m are reduced oxygen pressure and low temperature reduced cloudiness especially in winter high radiation intensity especially in ultraviolet reduced atmospheric humidity and almost complete absence of fog in the valleys a good wind protection and consequently a reduced

and very regular coolng power As to allergens we do not know enough Pollens certainly are less and different from those in the lowland But among my cases pollen asthma is quite exceptional Fungi are less frequent but are present and our mattresses and upholstered furniture contain as much dust as elsewhere Some information might be drawn from the effect on other allergic diseases I had to look after a restricted number of cases of eczema They improved considerably but the effect was less striking than in asthma and might be due at least partly to careful local treatment Among the Davos population eczema in children is rather frequent but asthma is quite exceptional although there are as I mentioned a considerable number of allergic families It seems so that the climate has not a general antiallergic effect but only an anti asthmatic one

Recently some investigations have been made on the influence of high altitude on the adrenal system Koller and his collaborators (Loeffler s clinic at Zurich) found at Jungfraujoch 3500 m that immediately after arrival the blood eosinophils dropped while the number of thrombo cyts and the excretion of 17 ketosteroids rose The effect was the same as that of an injection of ACTH but it was of short duration and lasted only a few hours The same tests by the same group were done at Davos The results were similar but less striking Recently by chance another fact pointing to the same conclusions was found Prader children s clinic Zurich was investigating the significance of the sodium/potassium ratio in the saliva as an indicator of adrenal function It is now clear that cortisone and ACTH depress this ratio Prader asked me for a series of samples just for investigating children with normal metabolism and endocrinologic pattern It turned out that the sodium/potassium ratio in our children was on an average somewhat lower than in normal children at Zurich In order to check these results further in a group of 20 girls who went to a camp in the mountains the saliva was examined before leaving immediately after arrival and 10 days later Again a significant drop was found that persisted at least 10 days These facts point to a possible mechanism but of course do not explain the whole of the curative effect For the present moment we have to refer as medecine has done for centuries to mere experience without being able to explain the pathophysiologic background

DISCUSSION

VARIATIONS OF BRONCHIAL ASTHMA UNDER THE INFLUENCE OF REGIONAL CHANGES WITHIN THE BRITISH ISLES

by

K MAUNSELL

Patients with bronchial asthma experience relief in the high mountains Such a drastic change however may not be needed in all cases It has been observed that in many instances freedom from attacks occurred within the British Isles themselves and thus within the general framework of the British climate

In a group of cases suffering from rhinitis with occasional attacks of bronchial asthma and living in Greater London a study has been made to check the variations of attacks under the influence of regional changes and whether or not a relation could be found between such variations and the soil of the region The patients histories were suggestive of the occurrence of attacks of asthma after exposure to one or multiple inhalant allergens such as house dust pollen and spores of fungi Skin tests with one or several of these allergens were frequently positive The attacks both of the nose and bronchi occurred in phases and the precipitating factors were closely linked the bronchial attacks however were more decisively marked than the nasal attacks Their abrupt onset followed by periods of complete remission impressed them on the memory of the patient Being thus landsmarks in the patient s history they seemed to provide evidence of the influence of regional changes on the patient The group studied consisted of 62 patients They came under observation whilst their residence was in the Greater London area Any regional change of more than a week s duration was noted and whether or not an asthma attack occurred during this change Some changes were holidays others were due to call up for service in the armed forces others permanent changes of residence Each regional change was counted irrespective of whether it represented an area already visited by other patients If however the same patient went more than once to the same area it counted as only one regional changes unless the patient reported that he was well on one occasion and had asthma on another in which case these findings were regarded as cancelling each other out The 62 patients of this group made 143 regional changes involving 110 different places The geological formation of these various places was checked by readings on a one inch to the mile drift map to ascertain the superficial strata

The regional changes were divided into those in which the patients were free from attacks and those in which patients experienced attacks

Results

1) Regional changes to alluvial areas 35 patients 46 areas
   a) In 41 out of 58 regional changes attacks occurred 71%
   b) In 17 out of 58 regional changes no attacks were reported 29%

2) Regional changes to clay area 31 patients 34 areas
   a) In 25 out of 40 regional changes attacks occurred 62%
   b) In 15 out of 40 regional changes no attacks occurred 38%
3) Regional changes to areas without alluvium or clay (mainly chalk gravel sand or rock) 30 patients 30 areas
   a) In 16 out of 35 regional changes attacks occurred 35%
   b) In 29 out of 45 regional changes no attacks occurred 65%

TABLE I

Reaction of patients to regional changes

To	Regional Changes	Attacks	Freedoms
Alluvium	58	41 = 71%	17 = 29%
Clay	40	25 = 62%	15 = 38%
Other Formations	45	16 = 35%	29 = 65%

Discussion

The influence of moist climatic conditions on bronchial asthma has frequently been stressed Recently Ordman (1955) reported the adverse influence on perennial bronchial asthma of climatic factors in the coastal areas of South Africa and showed that the significant climatic factor might be the combination of high atmospheric temperature and high relative humidity in constantly narrow range throughout the day and during the year The figures presented here for a small group of cases and the variations of their asthma in various regions of the British Isles also point to the influence of the relative humidity

The figures suggest that the precipitation or prevention of attacks may in part be determined by such climatic conditions as are generally referred to as relaxing —with an adverse effect—and bracing—with a favourable effect. The terms bracing and relaxing are not defined though many people are conscious of the bracing quality of open sea moorland and mountains According to G Manley (1953) relaxing qualities result from ground moisture combined with a high degree of humidity in the surface layers and and a lack of air movement to produce an interchange from above Such a hypothesis might well be adopted to explain the conditions prevailing in asthma precipitating areas on alluvium and clay soils These soils have a high moisture content especially after and during rainfall If the air is warmer above than below and no convection currents are present the moist packages of air rising from the ground cannot get away If this moist still air is polluted by allergenic particles an allergenic ground fog is formed and conditions seem set for an attack If on the other hand the soil

drains quickly as in areas of chalk and sand and low rainfall is combined with strong upward movements of air with slight air pollution many asthma patients find conditions for relief In England the Isle of Thanet with Margate Ramsgate and Cliftonville seems to give the best results and it may be that such conditions prevail on this island with its chalk ground and comparitively low rainfall

The exact address of each change of residence was not known and thus the precise position of the house in which the patient stayed could not be checked This may be of importance for the humidity or dryness of the house in which the patient stayed might have contributed to the general adverse or favourable effect of an area

SUMMARY

The highest incidence of attacks of bronchial asthma during periods of regional change was traced in areas with an alluvial soil Clay areas had the second highest frequency The lowest incidence occurred in areas without alluvium or clay as for examples areas predominantly chalk gravel sand or rock in formation

Acknowledgements

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I wish to thank Miss R Hobling B A for tracing the regional changes on geological maps which work was made possible by a grant from the Asthma Research Council

References

MANLEY G (1955) *Climate and the British Scene* Collins London

ORDMAN D (1955) *S Afr Med J* 29 173

ASTHMA AND THERMAL SPAS*

by

P SANGIORGI

Even in the remotest times—when a mineral spring was considered to be of divine origin and a temple was erected by its side in honour of the god who sent it and watched over it—men discovered the effectiveness ofs ome of these mineral springs in relieving a disease which they called something like spasm of the thorax and which nowadays is known as bronchial asthma Roman vestiges in Italy and Gallo Roman vestiges in France bear witness Besides most medieval chronicles report on the restorative action of several especially sulphurous springs But it was only during the 19th century that thermal hydrotherapy got over empirism and entered the stage of clinically and scientifically tested treatment

The curative limits of thermal hydrotherapy shall be outlined pre sently But before doing so it may be as well to examine the springs actually used for the treatment of the asthma syndrome the etiological pathogenetic and clinical polymorphism of which is apt to extend the vast field of our therapeutical efforts more and more

The principal anti asthmatic mineral springs are the sulphurous arsenous carbon gas chloro sodium and radio active waters

II

In sulphurous spas sulphur may be present under various forms namely free and perfectly visible (e g the ancient Roman Aquae Albule of milky appearance) gasiform namely represented by hydrogen sulphite with the typical bed egg smell in the sulphide hyposulphite or sulphate state or even in the colloidal state Sulphurous springs exist all over the European Continent and especially in Italy (Salice Terme Riolo Sir mione Porretta, Agnano Rome) France (Luchon Saint Honore Challes Aix les Bains) Spain (Lierganes Arechavaleta Alham de Granada) Germany (Lippspringe) etc

Sulphurous mineral springs supply the organism with the sulphur which as biological chemistry reveals has its share in the molecular structure of albuminoid bodies that in certain pathological conditions especially in chronic inflammatory or diathesic affections come to lag in the tissue of some organs And as we are aware that the broncho-pulmonary tissue the cartilaginous tissue the articular and skin tissues

Asthma and Allergy Research Centre at Salice Terme (Italy) headed by Professor P Sangiorgi

contain substantial quantities of sulphur sulphurous hydrothermal treatment is evidently efficient

Now do sulphurous spas exert a real anti allergic action? We are inclined to doubt it our own frequent laboratory tests with rabbits and guinea pigs and those of other workers always having been negative despite a certain if transient desensitizing action exerted by hyposulphite colloidal sulphur and sulphur solution due according to Lumière and Chevrotier to the inhibitory action of the drug on the flocculation of the colloidal fraction of the blood plasma or again to the antitoxic properties sulphur generally owns

Sulphurous hydrotherapy was found to exert a mitigating and equilib rating effect on the neuro vegetative system the irritability and in stability of which are the chief features of allergy in general and of asthmatic allergy in particular Experimental and clinical tests with regard to this system in all and any of its manifestations toning of the sluggish muscles pharmaco-dynamic tests oculo-cardiac reflexes humero tibial differential oscillometry artery tension rate of sedimen tation calcemic tests crinoreaction endocrin disturbance etc clearly evidence a sedative antispasmodic anticatarrhal action of the sulphurous spas

Thermal sulphur undoubtedly reduces organic combustion and devel ops a strong anabolic action thus fostering glycogen synthesis and increasing the liver glycogen reserve consequently toning up of the physiological liver function ensues while so far it was seriously obstacled by an insufficiency

Regarding direct action of sulphurous waters on the mucus of the respiratory apparatus we do not share the opinion of those who consider this action of secondary importance as compared with the above described general effects The Bolognese hydrology school admit local action of hydro sulphurous inhalations where congestive disturbances (present or past) or alterated cellular reactivity of the mucus of the respiratory apparatus permit penetration of allergens but at the same time attribute greater importance to the anti diathesic action than to the topic action of these waters

There is no doubt—and ancient as well as recent clinic experience supply ample proof—that the sulphurous waters greatly favour the local circulation of the respiratory mucus to which the aforementioned antiseptic antispasmodic and anticatarrhal actions are due Further more it is a wellknown fact that the pulmonary tissue holds substantial quantities of sulphur which however, belongs to the mucin namely to the secretion and excretion substance of the respiratory organs therefore one may suppose that one of the first stages of sulphur meta bolism must take place within these organs

There is then the action of sulphurous spas with regard to the skin and particularly to the keratin which accounts for their efficacy in the treatment of skin diseases that frequently accompany or follow asthma attacks They are particularly helpful in exudative and dry eczema

Finally the action of these very interesting and important group of spas with regard to the digestive system and biliar ducts the female genital mucus and the renal emunctory apparatus their anti rheumatic antitoxic antiluetic antiphlogistic actions are all apt to increase the field of their use more and more

III

Great importance is due to the group of arsenous and arseno-carbongas spas on account of their generally known intense anti asthmatic action where the French spas Mont Dore La Bourboule Saint Honoré etc hold the first place The Mont Dore waters are carbon gaseous bicar bonate ferrous arsenical highly silica holding spas the Bourboule thermal spring (40 to 60) is arseno ferrous and highly radioactive St Honoré spring is semi mineral sulphur sodic arsenical

The workers who dealt with those spas (Moncorge Galup Villaret Claude Besançon and many others) have now determined the physio logical action of those spas and their equilibrating action with regard to the humoral neuro vegetative and hormonal system of the asthmatic individual According to this research work a strong diathesic action is supposed to improve the constitutional complex of the asthmatic subject or the condition of a patient affected by asthmatic disturbance such as periodic or chronic spasmodic rhinitis spasmodic trachitis or wet bronchitis

The action of the arseno carbongas spas with regard to the liver is perhaps one of the most important features of the anti asthmatic treat ment considering that bronchial asthma is nearly always accompanied by more ore less accentuated liver disturbance (in 85 per cent of the cases according to Moncorge in 95 per cent according to me) and it is exactly to this more or less latent hepatism and consequent insufficient or altogether failing proteopexic function of the organ that the alteration of the humoral equilibrium in the asthmatic subject is due

The antispasmodic action of these arsenious or arseno-carbongas waters has also been experimentally tested in the isolated bronchial muscle by exposing it to the action of an acetyl-cholinic exciter

As regards a specific antiallergic action of this group of spas it must be said that they too like the sulphurous spas so far have not proved to be properly antiallergic and that quite a number of researches assert that they are not

IV

The chloride sodic spas with or without iodine as existing in various countries such as Germany, Austria Czechoslovakia and others are undoubtedly less efficient anti asthmatics than the sulphurous and arseno carbongas waters Still on account of the action of the sodium chloride they may be successfully applied in cases where the respiratory disturbance appears to be caused by alterated metabolism and call —although this is not definitely tested yet—for sodium chloride springs The iodine which sodium chloride often contains does not exert—at least in bronchial asthma—the curative effect the pharmacological iodine owns as a matter of fact sodium chloride spas were sometimes found to aggravate rather than alleviate the asthmatic trouble The cases these spas apply to shall be discussed later on

The anti asthmatic action of some of the French and Italian spas —Lurisia Thermae being the most important—has not been tested thoroughly in fact their efficiency has been established theoretically while clinical data are scarce

As is wellknown the essentially radioactive springs are generally poor in mineral substances and their principal action was found to be alteration of the uric acid metabolism where their sedative effect on the central nervous system and their analgesic action on the peripheric nerves is considerable In cases of bronchial asthma of uricaemic origin where asthma attacks alternate with gout and hemicrania attacks or with renal or liver lithiasis and which were decreed to be local colloido clasic disorders—respiratory articular, vascular or cutaneous— radio active waters really have sedative and antispasmodic and probably (now being researched) also anti anaphylactic effect

V

It appears that only sulphurous waters and arseno carbongas waters can be relied upon for bronchial asthma treatment where it must be of course understood that any hydrotherapy is only an additional if excellent and efficient treatment of bronchial asthma Personal experience permits me to consider mineral hydrotherapy especially the therapies based on sulphurous or arseno carbongas spas the asthmatic patient s most reliable ally in a battle against his disease fought with modern sedative diathesic specific or aspecific dietetic and other cures

The clinical forms of bronchial asthma calling for hydrotherapy are pure bronchial asthma and wet asthma be the patient young or old be the outbreak of the disease recent or years back

The above described physiological effects of the spas are indicative for the choice to take in the individual case sulphurous waters apply to wet

asthma especially to the chronic or post bronchitis affections where pulmonary sclerosis or bronchoectatic processes set in they also apply to asthma of luetic origin and to asthma following skin diseases of the turpid type to chronic colds sinusitis and rheumatic affections

For pure asthma of established allergic origin sulphurous spas are effective only inasmuch these waters improve the mucus condition in the respiratory apparatus which after thermal treatment can delay but not prevent the allergens attack There are a few more advantages to be obtained with regard to the neurovegetative system the liver and the other diathesic conditions

In pure asthma that cannot be called allergic (and here the 19th century neurogen theory was readopted after the exaggerated enthusiasm roused by the new allergy theories had passed) the neuro vegetative balancing action both vagal and sympathic fully account for the good if limited results as above stated of the sulphurous spas

These indications also refer to the arseno carbongas spas on account of their antispasmodic sedative anticatarrhal trophic actions These spas that like the sulphurous spas are not really antiallergic cater for pure and dry asthma spasmodic rhinitis spasmodic tracheo bronchitis asthma in lymphatic sluggish anaemic children affected by adenoidism and tracheo bronchial adenopathy and for asthma complicated by car dial vascular disorder

Regarding sodium chloride and radioactive spas that do not act direct on the respiratory system but have a diathesic effect it can only be said that their use is just a coadjuvant in the treatment of bronchial asthma caused by neuro arthritic hormonal or uricaemic affections that permit treatment with these waters in combination with sulphurous or arseno carbongas spas Chloride bromo iodic spas for instance applied to gether or immediately after sulphurous spas have proved effective in many cases of asthma due to ovarian or thyroid disorders

Hydrothermal cures are counter advised if the status asthmaticus is due to neoplasms in the respiratory system evolving tuberculosis of the lungs acute infectious or contagious diseases of the airways heart diseases with insufficiency or a tendency towards insufficiency etc

VI

Hydrotherapy for bronchial asthma is effected in all available forms above all inhalatory namely wet inhalation dry nebulization aerosol humage

Inhalation introduces the mineral components of the waters direct into the respiratory apparatus with a topic effect that in many cases may be termed radical with regard to relieving chronic sluggish dystrophic

inflammatory disorders in any level of the respiratory system together with sedative and antispasmodic action as numerous laboratory tests have confirmed

Besides the topic effect of inhalatory cures it was found that through the respiratory system general absorption takes place at a rate comparable with intravenous injections, which explains the effectiveness of mineral water inhalation in the various parts of the human organism

Complete mineral water baths which in the treatment of asthma were rather neglected in the past while the inhalation method was definitely preferred gained new ground of late as they not only proved nearly as effective as inhalation treatment but in certain cases are even more helpful Recent researches have in fact shown that the skin can absorb the principal chemicals solved in the mineral bath so as to form a complete coating the biological action of which is obvious considering the existing co-relation between skin and organism Besides during the mineral baths certain electric ionophoresic and also other phenomena arise which however cannot be discussed here

The curative effects of oral administration of mineral waters or again irrigation treatment in bronchial asthma are of very scare account still such treatments may relieve other disorders connected with the asthmatic patient s condition

During these last few years subaqueous clysters were experimented on a large scale and it was found that they are almost as effective as full baths

Hot thorax compresses Scotch showers consisting in alternating hot and cold jets of water hot baths subsequently cooled for 1 or 2 minutes pertain to the simple hydrology technique and as they act by virtue of their physical mechanism (Martinet compares them with vaccination through physical agent) they are usually applied with non mineral water Their relieving effect with regard to bronchial asthma is sometimes quite astonishing as their vasomotoric action may even succeed in re-establishing the neuro vegetative equilibrium in the asthmatic individual

VII

Finally there is the prophylactic action the sulphurous or arseno-carbon gas spas can achieve in individuals who on account of a delicate respiratory system easily contract colds or bronchitis and therefore are threatened with bronchial asthma especially if they come from families where cases of bronchial asthma pollinosis or other allergic affections occurred

The writer on the ground of his personal medical experience with the sulphurous springs at Salice Terme is of opinion that this very interesting feature of thermal hydrotherapy deserves profound study and investigation

DISCUSSION

R ALEMANY VALL

Twenty years ago I have studied (for two years together) with Dr Claude at the thermal hospital of Mont Dore the influence of a course of waters (thermal waters) on 108 asthmatic patients

The research of the blood eosinophiles of the cholesterine of the urine acid of the oculo-cardia reflex before and after the treatment

We were able to state the good and definite influence of this on the eosinophiles and the oculo-cardia reflex

With some patients of Barcelona and those I have been able to observe in the hospital of Mont Dore where I worked for several years I have stated a good result in a great percentage of those diseases which by their clinical history and examination of allergens did not show any hyper-sensibility to a determined exterior allergy

We think that the thermal waters of Mont Dore have an unspecific desensibilization absolutely independent of the height at which these thermal waters are situated

PREVENTING MEASURES*

by

KNUD WILKEN JENSEN

Twenty four years ago Rowe stated that second only to infection allergy was the most important single etiologic agent in human symptomatology and just as we try to prevent infective diseases it is worth while considering prevention of allergic diseases

This problem may be approached and attacked from different view points and as the first one I have chosen the genetic or hereditary in fluence I am quite aware that no complete agreement exists about this question but most authors seem to consider it a fact that asthma—or the disposition to asthma—is inherited According to Schwartz two asthmatic parents will have at least 20—25 per cent chance of having children with asthma and if one child in the family has asthma the probability will be much grater

If only one of the parents is an asthmatic patient the percentage of asth matic children will probably go down to about 13 per cent But another part of the children will in both cases have other allergic manifestations

Glaser has found 60 per cent children with major allergic diseases before the age of ten This may be taken into consideration if two asthmatic patients want to marry and plan to have children

Ratner has disputed the significance of heredity and attached much importance to the pregnant mothers diet A few examples which make the sensitization in utero likely have been published but the paper by Bowen about allergy in identical twins does not give any support to this view and it appears to me to be rather doubtful

The next point is the elimination By this I do not mean the elimination diet which we heard about yesterday but a potentially allergic child may be protected against several allergens thus avoiding the possibility of being sensitized The child must be immunized against the different childhood infections because experience tells us that they may act as the initiating or aggravating mechanism and great care must be taken to avoid exposure to especially pertussis as this seems to be the worst of the common infections It is especially important to immunize against tetanus as the tetanus antitoxin usually is made from horse serum which may be dangerous to the patient If an asthmatic or potentially asthmatic patient has been infected antibiotics should be administered

From the Out Patient Clinic for Children with Allergic Diseases R gshospitalet Copenhagen

to a greater extent than usual but it may be of value to vary the remedy in order to avoid drug allergy

An important thing is—as you all know—toc onsider the environment of the asthmatic or potentially asthmatic patient The bedroom should contain as little furniture as possible and especially have as few dust collecting things as possible The bed should have no ordinary mattresses or pillows unless these are enclosed in dust proof plastic casings But it is perhaps wiser to use sponge rubber or the mattress may be filled with paper in small bits the cover can be woollen blankets which must be washed frequently and the pillow may be replaced by a great towel in the casing so that they can be washed too Anything with feathers and silk must be abolished and of course no animal pets are allowed at least if the allergy is of a disabling type

With regard to food Glaser postulates that it is of value to give babies in allergic families soybean milk instead of cow s milk if the mother cannot or will not nurse her baby He claims that a far smaller part of the soybean milk fed babies developed an allergic disease than the controls His paper seems to be the only one published of this kind

I do not intend to give you all the details of the way in which a child s or perhaps rather an infant s diet should be varied and altered according to reactions and age but only mention that any new kind of food should be given in small and gradually increasing amounts

But another thing is that it is often unwise to force a child to eat some food which it does not like as it often seems to be a kind of food to which it is reacting if tested

Speaking about elimination it may be worth while mentioning the advantage of occupational guidance before entering a profession

I do not believe in the value of so called hardening processes as cold showers diving into cold water and sleeping in cold rooms nor do I consider the different systems of respiration exercises as being of any great importance

I have tried to let some of my patients learn respiration exercises and some others to learn relaxation exercises but only very few seemed to benefit from it and I wonder if these treatments are of more than psy chological significance

By this I do not want to indicate that I underestimate the significance of the psychological side of the prevention Quite on the contrary I look upon it as very important I always teach parents and relatives to the patients to treat them as normal healthy individuals but of course with out forgetting their individual hypersensitiveness The more they are surrounded by fear overprotection and prohibitions the more the patients feel themselves abnormal weak and second-class persons and the more attacks do they develop If a patient is warned against doing

one thing or another he will not be certain that he could not endure it but if he is allowed to try and fails he is convinced and likely to try much more to get rid of his weakness Away from the usual surroundings patients will often stand many physical exertions which would be im possible at home in the asthma minded atmosphere So if it is possible to lessen the tension the aggression and the anxiety of the family all the psychologically provoked attacks may be abolished

If a patient knows that he has to go to a place where he is likely to develop an asthmatic attack he may be able to prevent it by taking one of the many antihistaminic drugs but their effect is rather unreliable in asthma

In other cases he may be protected by taking ephedrine 3—4 times during the day or a prescription which we use very much instead of pure ephedrine as it seems to be tolerated better and have the same effect It consists of

Phenacetin	
Theophyllin $\overline{aa}$	ctg 5
Coffein	mgm 25
Ephedrine hcl	
Extr belladonn $\overline{aa}$	mgm 5
Agaricin	mgm 1 25

PSYCHOTHERAPY IN ALLERGIC PATIENTS*

by

B STOKVIS AND A J WELMAN

A) INTRODUCTION

When we speak of psychological therapy or better still of psychotherapy for those who suffer from allergic disturbances we postulate that in fact no differences exist between the various forms of therapy that we are dealing with therapy as such Still the human being and thus also the sick individual should be considered as a mind matter entity—a psy *chophysical totality with a free mind*

The mental need in which a sick person finds himself must not be underestimated—regardless of whether the illness be determined pre dominantly by mental or by somatic conditions—such an individual is still a person in distress

This concept is in fact already expressed in the suggestive manner in which even the non psychologically oriented physician administers medicine—each medicament having in addition to its pharmaco-dyna mic action a psycho-dynamic one The latter is dependent not only upon the nature of the drug and the method of administration but also upon the particular relationship that exists between the doctor and the patient—the so-called transferance situation

Psychotherapy is an attempt to psychically influence the sick in dividual—that structured living totality with a free mind Its purpose is to cure or in a given case to relieve or actively control the suffering

While psychotherapy was originally almost exclusively directed to ward patients with mental disturbances during the last ten or fifteen years the indications for psychotherapy have broadened Those diseases which previously were considered as exclusively somatic the so called psychosomatic disturbances also belong to the indication sphere of psychotherapy

At the Leyden Psychosomatic Center we include under psychoso matic disturbances all diseases which are expressed in the bodily sphere and for the appearance of which emotional factors in the present or past are responsible Utilizing this broad definition it is no longer necessary to limit the concept of psychosomatics to the complex of psychosocial diseases such as Asthma Ulcer Colitis Anorexia nervosa Coronary Artery disturbances Migraines and Hyperthyroidism—as did

From the *Psychosomatic Center* State University Leyden.

Halliday [26] These diseases we group under the collective title of Somato-Neuroses —this in contra distinction to psycho neuroses (neurotic phenomena in which mental disturbance is noted) In addition to the somato neuroses we distinguish somato psychoses (psychotic disturbances which are expressed in the bodily sphere) Moreover, we also consider conversion hysterical reaction forms organ neuroses and vegetative neuroses in the same group as psychosomatic diseases (namely somato neuroses) Patients with chronic somatic diseases to which they react in a neurotic manner are also entitled to psychotherapy and for that reason are considered as having a more or less psychosomatic disturbance

I NEUROSES
- A) *Psycho Neuroses*
  1) Hysterical Neuroses (among others conversion hysterical reaction forms)
  2) Compulsive Neuroses
  3) Neurasthenic Reactionforms
- B) *Somato Neuroses*
  1) Psychosocial diseases (so called psychosomatic disturbances sensu strictiori)
  2) Organ Neuroses
  3) Conversion Hysterical Reactionforms
  4) Vegetative neuroses

II PSYCHOSES
- *a)* Psychoses sensu strictiori
- *b)* Somato psychoses

III SOMATIC DISTURBANCES (neurotic reaction to chronic disease)

IV NERVOSITY (constitutional disturbance with vegetative phenomena)

Application of psychotherapy to psychosomatic disturbances in the broad sense of the term is aimed at treating the emotional determinants which condition the somatic illness Lately the attempt is being made not only to influence the affective factors but at the same time to reach the sick individual himself—to subject his place in the world to closer scrutiny (von Gebsattel [2] Caruso [11] Frankl [0])

In psychotherapy as in somatotherapy a scientifically justified set of indications is indispensable

This set of indications for therapy is dependent on three factors the nature of the disease the personality structure of the patient and that of the doctor While choice of therapy in somatic disturbances is decided by the nature of the illness in psychotherapy the decision depends upon

the personality structure of the patient and of the doctor In order to learn the patient s structure we utilize structure analysis with the aid of psycho diagnostic investigation For this purpose the results of the tests are arranged in terms of the five facets of personality as described by Carp [9] (Drives and Temperament as biological basis intelligence and psychomotor with character as keystone) In our Psychosomatic Center we use the following battery of tests routinely the Wechsler Bellevue test the Rorschach test the Szondi test the Thematic Apperception test the Four Picture Test Wartegg test and the House Tree Person test

The indication for psychotherapy in psychosomatic diseases depends on the results of the psychosomatic investigation as a whole—in other words it depends on the results of the biographical the psychohygienic the physiopsychological the socio psychological the psychiatric and last but certainly not least the somatic investigations

B) PSYCHOTHERAPEUTIC METHODS

We will now briefly elucidate some of the psychotherapeutic methods These are broken down into individual treatment methods and methods whereby the patients are treated in a group

The methods of treating the individual consist of the covering (non exploratory) and the uncovering methods as well as the psychagogical methods (see table 2) In the covering methods the psychic factors which condition the disease are not sought—these actually being pushed still deeper (into the unconscious) (repressed) The uncovering methods pre suppose a causal etiological therapy The factor causing the illness is here unearthed is interpreted and thanks to the enlightened insight that the patient obtains the damaging action of the earlier psycho traumatic event is eliminated In the psychagogical method the patient is shown how best to direct and lead his future life

The covering methods utilize suggestion and auto suggestion—while hypnosis acts as a bridge between the covering and uncovering methods The uncovering methods include hypno catharsis narco analysis (drug psychotherapy) in addition to the methods of Freud Jung and Adler

Psychagogic treatment can be administered as a re education This requires self education though suggestion can also be utilized For this purpose behavior patterns are drummed into the patient s head

In group therapy mutual exchanging of ideas between patients is encouraged (group discussion) moreover the varying attitudes of patients executing a joint work project is utilized (activity groups) It is also possible to study the reactions of the patients during a popular lecture (didactic groups) In the psychotherapy depicted psycho-drama and finger painting are chosen as starting points for emotional expression

In this connection we must also include socio therapy which acts to stimulate a feeling of responsibility in a community of patients (Carp [10] Daumézon [14 15 16] Sivadon [63 64 65])

Case work whereby the social worker helps with the therapeutic difficulties deserves separate mention In 1922, Mary Richmond gave the following description of this Processes which develop personality through adjustments consciously effected individual by individual, between men and their social environment

In 1953 the Commission for Social Hospital work defined case work in the following manner The aim of case work is to study the social (personality and environment) factors in the life of the patient in conjunction with the doctors concerned in order to obtain insight into the connection between the development and course of the disease and in addition to attempt to alter these social factors in order to promote recovery and to prevent relapse

Naturally social therapy is important in the treatment of psycho-social diseases

Before discussing our own experiences with psychotherapy in asthmatic patients we shall first summarize the pertinent literature *

C) SURVEY OF THE LITERATURE CONCERNING PSYCHOTHERAPY IN ASTHMA

This literature has by this time become very extensive the different authors seem to prefer diverse psychotherapeutic methods Many investigators use the word psychotherapy in general without precisely describing the method used Most publications scarcely mention any figures It is noteworthy that in important clinical works on asthma such as that of Cooke Feinberg [19] Hansel [27] Vaughan [77] little or no mention is made of psychotherapy We shall try, in so far as possible to arrange these literary excerpts according to the forms of psychotherapy employed

I THE SIGNIFICANCE OF PSYCHOTHERAPY IN GENERAL

Long ago Hippocrates [31] discerned a connection between bronchial asthma and emotions and made use of this connection in his treatment of this condition Also several 7th century commentaries discuss the importance of psychotherapy in bronchial asthma Two 17th century authors Henry Hyde Salter [57] and John C Thorowgood [74] pointed out in their own ways how a conversation could act as a curative agent

The connection between the mind and allergy in addition to the psychological aspect of bronchial asthma need not be discussed here The literature on this subject is extensive

F Reichmann [53] (1922) described bronchial asthma as a neurosis on a psychopathic base She deems psychotherapy the mainstay of the treatment—with drugs as an eventual adjunct She is concerned with the how and not the what in the treatment of asthmatics

E Moos [46] (1923) discusses seven patients who were cured with psychotherapy where somatotherapy had failed Those patients whose sputum previously had contained Curschmann s spirals and Charcot Leyden crystals now had sputum which was negative for these In two cases approximately 200 cc of sputum were produced daily—this symptom also disappeared completely The eosinophilic blood picture returned to normal In a later article (1928) [47] he describes 16 patients with definite somatic symptoms who were cured

Using psychotherapy J Loewenstein [37] (1926) noted a definite im provement or cure of 60—70 per cent of a group of 48 asthma patients Among other things he pointed out the importance of the psycho analytic method

Psychotherapy is also considered of great importance in bronchial asthma by C Romer and A Kleemann [55] (1927) They describe 10 patients with extensive somatic symptomology who reacted favorably to psychotherapy whereas somatotherapy had had little or no success One patient showed a decrease from 24 per cent to 4 per cent in eosinophil cells in the peripheral blood

Pollnow Petrow and Wittkower [51] (1929) as a result of their expe riences with 45 patients prefer psychotherapy They chose a therapy giving insight in preference to hypnosis because the former method is more causally directed

Other authors who recognize the importance of psychotherapy are Gottlieb [23] Kronfeld [34] F Mohr [43] and Unger [6] Mohr in a later publication [44] (1949) [45] (1954) points up the significance of an analytic aspect in this therapy

E G Billings [6] (1947) discusses the treatment of 17 cases of psychogenic asthma He was successful in 6 of these cases—but does not indicate the method he used

Further more Freuting and Ripley [21] (1948) discuss the use of both somatic and psychic therapy in a number of patients The group of 24 who received psychotherapy over periods of time ranging from several months to 2 years responded most satisfactorily of all In one instance hypnosis was used with good result

In Holland Van Lookeren Campagne [38] (1950) and Quarles van Ufford [5] (1950) and others stress the importance of psychotherapy —especially in children The former points out that while such treatment is important for curing asthma bronchial qua talis it is in addition important for the development of the child s personality

Various authors consider the combination of allergic and psychotherapeutic treatment of value Abrahamson[2] (1951) E A Brown[8] (1951) E Weiss[78] (1950) Groen[25] and others use a combined treatment of ACTH and psychic influence

II THE SIGNIFICANCE OF UNCOVERING METHODS OF TREATMENT

We can divide this methods into 4 groups

1) *Psychoanalysis*

In his publications[28] (1927) [29] [30] (1929) [31] (1930) Hansen appears to be very critical of the value of psychotherapy Still he considers psychotherapy necessary in a number of cases He feels however that only the analytical method is important He considers hypnosis as less desirable Abrahamson[1] (1948) discusses a number of patients who reacted favorably to psychoanalysis In the Netherlands Bastiaans[5] *also used the psychoanalytic method on a number of patients—and* furthermore considers the so-called short therapy useful in asthmatics

2) *The Short Therapy*

This method was introduced by Alexander[4] [3] and French[3]

It gives the patient an opportunity at catharsis in several sessions The patient is given insight into his problems through analytical means Levine[36] (1952) describes a boy who lived in an iron lung and could not dispense with it for more than 3 to 5 minutes at one time This however did not agree with the somatic condition After a short conversation an anxiety element was uncovered and the boy was able to remain out of the iron lung for an entire day One of us[67] (1953) discussed a 51 year old patient who had suffered from bronchial asthma for 15 years Using a short psychotherapy in the form of a combination of insight uncovering and cathartic treatment together with relaxation therapy (Active relaxation) we obtained good results with this patient Zoss[79] describes a patient in whom an anxiety situation cleared up in three sessions

3) *Catharsis*

Some writers indicate that catharsis alone can work therapeutically Experience has shown even the non psychotherapeutists how the relating of one s life history can work to relieve tensions This fact was pointed out by Naber[49] in 1929 and again by Miller[39] and Skands[66] in 1951

In this connection the non directive psychotherapy of Rogers[54] can be mentioned Mitchel[41] (1946) and, later Mitchel[42] Curran and Meyers (1947) treated a number of patients using this method with good results A special form of catharsis is that brought about under the influence of hypnosis or drugs (the so-called drug psychotherapy) This method was described by Cohen[1] (1946—The narcoanalysis of 2 women)

4 *Other Methods*

In our Psychosomatic Center we use other uncovering methods when indicated These include the individual psychologic method of Adler and the psychagogic treatment of Kronfeld [31]

III THE SIGNIFICANCE OF THE COVERING METHODS OF TREATMENT

1) *Autogenic Training*

I H Schultz [58 61] the initiator of this method has this to say about it Es ist dies die ubende Erlebung einer Selbstumschaltung die sich durch bewusste Zuwendung auf das Endosensorische bei Aussenreizverar mung Immobilisation mit Entspannung systematisch entwickelt Schwoebel [6] (1948) noted an average increase of 500 cc in vital capacity using this method (combined with massage and with breathing excer cises) He obtained good results in 42 of 50 patients Trautwein treated 40 patients with this training and obtained distinct improvement in 95 per cent In 50 per cent the asthma disappeared completely Many other investigators have obtained good results with

2) *Hypnosis*

One of us [69 0] has had favorable experiences using hypnosis in asthmatics Schultz [59 60] obtained favorable results with asthmatics whose sputum contained Curschmann s spirals In 1910 Brugelmann [7] described this method Laudenheimer [3] successfully combined this method with breathing excercises in 1926 Flanders Dunbar [18] described a patient of Costa s in her book Despite serious somatic symptoms this patient was cured

3) *Relaxation Therapies*

Groen [24] (1946) Ross [56] and Wilson and others described the signifi cance of these methods They emphasize the significance of crying in the treatment of asthmatics and the relaxation of their ability to do so in psychotherapy is frequently followed by great relief of symp- toms

4) *Suggestion*

This also has important therapeutic significance Tagerberg [3] (1953) describes how he substituted physiologic saline injections for ACTH in patients requiring ACTH and still obtained the same subjective results (Somatic symptoms such as rales and eosinophilia remained unchanged) Dees [17] also stressed the significance of suggestive factors

5) Finally *Mechanization* has made its appearance in psychotherapy Morwood [49] makes use of a gramophone in asthma A method of inducing a state of semi hypnosis by a formula of words given by gramaphone Naturally this method is a modification of the suggestive —autosuggestive method

As the last group of therapy we turn our attention to

IV THE SIGNIFICANCE OF GROUP PSYCHOTHERAPY

Miller and Baruch [40] discuss the favorable results obtained in several asthmatics using group treatment Groen [25] also, obtained results with this method

D) OUR EXPERIENCES WITH PSYCHOTHERAPY IN ASTHMATICS

The following is an account of our experiences in the Leyden Psychosomatic Center [0, 71] We are here concerned with 80 asthmatic patients who were examined by us since the establishment of the Center in January 1952 Of these psychotherapy has thus far been used in 30 cases

Following the methods and theories advocated in our Center, we treated the patients with either the uncovering or the covering methods From the first group we selected cathartic analysis the short therapy, and where indicated the method of Adler In spite of being convinced of the supreme place occupied by Freud s psychoanalysis in many cases we were thus far forced to abandon a systematic application of it due to varied circumstances Hypno-catharsis was used in several cases where an actual conflict situation existed and where connected affective tension was present

Of the covering methods we used hypnosis and relaxation therapy on asthmatics in our Center Of the various relaxation methods we used Schultz s autogenic training and also active tonus regulation—which is customarily used in our Center Naturally suggestion in the form of administration of placebos was used in many cases Recently Pflanz [50] formulated an important explanation of this form of pharmaco psychology In diverse cases the psychagogic treatment was used in order to present the patients with aspects and perspectives of life Where the intelligence was insufficient it was necessary to abandon re education in the sense of self education and utilize suggestive or even hypnotic methods (Kretschmer) [33] in order to accomplish re education

In addition to the individual treatment 40 per cent of our asthma patients were treated with group therapy—group discussion and psycho and socio drama were the forms of group therapy used

Those patients admitted to the hospital were in addition treated socio therapeutically in conformance with the newer points of view (see Carp [10] Daumézon [14, 15, 16] Sivadon [63, 64, 65]) In socio therapy an appeal is directed at being responsible to each other and for one another Further more attempts are made to extract the patients from a fettered relationship in which there is a feeling of dependence upon one another and to supplant this with an associative relationship based on attachment to one another In order to bring this about the so-called Patronage Principle of Carp [10] is employed

TABLE 1

Psychosomatic diseases viewed pathopsychologically

I NEUROSES
- a) *Psycho-neuroses*
  1 Hysterical neuroses (incl conversion hysterical reactionforms)
  2 Compulsion neuroses
  3 Neurasthenic reactionforms
- b) *Somato-neuroses*
  1 Psychosocial diseases
  2 Organneuroses
  3 Conversion hysterical reactionforms
  4 Vegetative neuroses

II PSYCHOSES
- a) *Psychoses (sensu strictiori)*
- b) *Somato psychoses*

III CHRONIC SOMATIC AFFECTIONS
with neurotic complication

IV NERVOSITY
constitutional disease with vegetative symptoms

TABLE 2

Psychotherapy applied in asthma patients

I *Individually applied*
- a) Covering Psychotherapy
  Suggestive Methods
  Auto suggestive Methods
  (relaxation)
  Hypnosis
- b) Discovering Psychotherapy
  Hypno catharsis
  Narco analysis
  Psycho analysis (Freud)
  Individual Psychology (Adler)
  Complex Psychology (Jung)
- c) Psychagogic Psychotherapy
  Re-education (Kronfeld)
  Suggestive psychagogic

II *Groupswise applied*
- a) Discussion therapy
- b) Activity group
- c) Didactic group
- d) Psycho-drama Finger painting

In many cases finger painting is used by way of experiment as an expressive form of psychotherapy This treatment acts to relieve tensions and the drawings sometimes offer the therapeutist important clues in support of the individually applied uncovering therapy

In conclusion we shall present the results of the various treatments used The criteria suggested by Groen [25] and Orie were used in judging our results These include subjectively perceptible wheezes objective symptoms and complaints of the patient In most cases (66 per cent) a combination of psychotherapy and somatotherapy were employed As the psychotherapy made progress the somatic treatment was gradually decreased The results can be summarized as follows

Using uncovering treatment all the patients showed some improvement and with covering therapy 85 per cent of the patients improved

TABLE 3

Results psychotherapy bronchial asthma patients

Form of psychotherapy applied								Degree of improvement		
Individually						Groupswise				
Discovering (13)		Covering (11)		Psychagogic (6)		Discussion Psycho Drama (13)		Complaints	Subjective wheezing	Objective findings
No	/*	No	/*	No	%*	No	/*			
2		4		3		1		—	—	—
5		2		1		6		—	—	slight
2		2		2		2		slight	—	wheezing
4		3		–		4		rising	wheezing	wheezing
–		–		–		–		non rising	Status asthmaticus	

Number of patients too small

A catamnestic investigation revealed of those that responded that the improvement in most of the cases remained constant The control time varied between ½ and 3 years

It is interesting to compare these results with those obtained by one of us employing psycho-therapy in psychoneurotic patients [63] When one bears in mind that asthmatics are in essence patients with somato neuroses one will not be surprised that the respective results are more or less similar

Our conclusions indicate that in the light of present day opinion application of psycho therapy to bronchial asthma sufferers must always be considered Let us hope that with this consideration as starting point we shall be able in the near future to completely bridge the old unjustifiable gap between allergologists and psycho therapeutists We must not forget the object of this address is and remains the human being who due to the Cartesian Teaching of diaschizis has for centuries been unjustly separated into body and mind In accordance with our present day opinions on that subject he is a psychosomatic totality—and as such when sick deserves to be psychosomatically treated

Refe e ces

1 ABRAMSON H A Psychodynamics and allergic pat ents *Ann Allergy 6* 219—2.3 (1948)
2 — *Psychodynamic pharmacology in the therapy of asthma* New York (1951)
3 ALEXANDER F FRENCH T *Psychoanalytic therapy* Ronald Press Co New York (1946)
4 — *Psychosomatic medicine* New York.
5 BASTIAANS J Problemen b j de psychotherapie van psychosomatische ziekten Ned Ver voor Psychotherapie *Ned T Geneesk 98* 1730 (1954)
6 BILLINGS E J Dynamic and therapeutic features of 17 cases of so-called psychogenic asthma *Rocky Mtn med J 44* 197 (1947)
7 BRÜGELMANN R *Das Asthma* Sein Wesen und seine Behandlung auf Grund zweiund dreissigjähriger Erfahrungen und Forschungen dargestellt Bergmann Wiesbad n 5 verm Aufl 267 (1910)
8 BROWN E A Combined allergic and psychosomatic treatment of bronchial asthma *A n Allergy 9* 3.4 (1951)
9 CARP E A D E *Med sche psychologie en pathopsychologie* Scheltema & Holkema 2e druk Amsterdam (1951)
10 — *Sociotheropie* De Tijdstroom Loch em (1954)
11 CARUSO I A *Psychoanalyse und Synthese der Existenz* Herder Heidelberg (1952)
12 COHEN S Psych c aspects of asthma *Intern Con Notes X 2* (1946—1947)
13 COOKE R *Allergy in theory and practice* W B Saunders Comp Philadelphia and London 548 (1947)
14 DAUMÉZON G Actions individuelles de la psychothérapie collect ve *L é olution psychia trique 3* 475 (1952)
15 — Le journal parlé de l hôpital psychiatrique *An èe médico-psychologique 1* 62 (1950)
16 — Les fondements d une psychothérap e collective *L évolution psychiatrique 3* 57 (1948)
17 DEES S Inter relat onships of allergic and psychiatric factors in allergic children *Proc Twelfth Int Child Research Cli ic of Woods School 59* (1945)
18 DUNBAR F *Emotions and bodily cha ges* Columbia University Press New York (1954)

19 FEINBERG S M *Allergy in practice* The Year Book Publishers Chicago (1946)
20 FRANKL V E *Logos und Existen* Amandus Wien (1949)
21 FREUTING TH RIPLEY M S Life situations emotions and bronchial asthma *J nerv ment Dis 108* 380 (1948)
22 GEBSATTEL V E V *Prolegomena einer medi inischen Anthropologie* Springer Berlin (1954)
23 GOTTLIEB PH M *Ann of Allergy 12* 469
24 GROEN J Psychosomatische aspecten van asthma bronchiale *Ned T Geneesk 97* 1946 (1953)
25 — Behandeling van asthma bronchiale met de combinatie van ACTH en groepspsychotherapie *Ned T Geneesk 98* 2212 (1954)
26 HALLIDAY J L *Psychosocial Medicine* Heinemann London (1948)
27 HANSEL FRENCH T *Cli ical Allergy* C V Morby Company St Louis 606 (1953)
28 HANSEN K Analyse Indikation und Grenze der Psychotherapie beim *Bronchialasthma Ber ub d II allg ärztl Kongr f Psychother* Hirzel Leipzig 195—199 1927 Also *Dtsch med Wschr 55* 1462—1464 (1927)
29 — Allergic and psychical factors in asthma *Proc Roy Soc Med 22* 789—800 (1929) (Abstr *Lancet I* 443444 (1929))—
30 — Zur Frage der Psycho-oder Organogenese beim allergischen Bronchialasthma und den verwandten Krankheiten *Nervenarzt 2* 633—641 (1929)
31 — Zur Frage der Psycho-oder Organogenese beim allergischen Bronchialasthma und den verwandten Krankheiten 2 Ueber psychische Bedingungen des Bronchialasthmas *Nervenarzt 3* 513—523 (1930)
32 HIPPOCRATES *Translations of the Aphorisms* (FRANCES ADAMS)
33 KRETSCHMER ERNST *Medi inische Psychologie* Thieme Stuttgart 10th ed 277 (1950)
34 KRONFELD A Ueber Psychotherapie gestörter Organfunktionen Indikation Gegen indikation Methode der Wahl *Ber ub d II allg ärztl Kongr f Psychother* Hirzel Leipzig 89—105 (1929)
35 LAUDENHEIMER R Hypnotische Uebungstherapie des Bronchialasthmas *Therap der Gegenw 67* 339—344 (1926)
36 LEVINE M *The impact of psychoanalysis on training in psychiatry* A paper read before the Twentieth Anniversary Scientific Meetings of the Institute for Psychoanalysis Chicago (1952 Oct 11th)
37 LOEWENSTEIN J Asthma und P ychotherapie *Med Klin 22* 944—947 (1926)
38 LOOKEREN CAMPAGNE J v Asthma boven de Zu gelingenleeftijd *Ned T Geneesk 94* 646 (1950)
39 MILLER M L Emotional conflicts in asthma *Dis Nerv Syst XIII* No 10 (1952)
40 MILLER M L BARUCH D W Psychotherapy in acute attacks of bronchial asthma *Ann Allergy 11* 438 (1953)
41 MITCHEL J H CURRAN C A A method of approach to psychosomatic problems in allergy *West Virginia M J 42* 1 (1946)
42 — — and MEIJERS Some psychosomatic aspects of allergic diseases *Psychosom Med 9* 184 (1947)
43 MOHR F *Psychophysische Behandlun smethoden* Hirzel Leipzig 493 (1925)
44 — Ueber die Beziehung psychischer Vorgange zu Allergischen Sonderdr a d *Verhandl d dtschen Gesellschaft f inn Medizin* Wiesbaden (1949)
45 — Die psychophysische Behandlung allergischer Krankheiten *Acta Psychotherapeutica I* 220—231 (1953)
46 MOOS E Kausale Psychotherapie beim Asthma bronchiale *Munch med Wschr 70 805—808 (1923)*
47 — Zur Behandlung des Asthma bronchiale *M nch med Wschr 75* 1841—1842 (1928)
48 MORWOOD J M B Relaxation by gramophone in asthma *Practitioner 170* 400 (1953)
49 NABER J Asthma bronchiale Allergische Behandlung und Psychotherapie *Therap d Gegenw 70* 437—442 (1929)

50 PFLANZ M Zur Methodenlehre der Pharmakopsychologie *Ztschr f exp u angew Psychol 2* 514—551 (1955)
51 POLLNOW H PETROW H WITTKOWER, E Beiträge zur Klinik des Asthma bronchiale und verwandter Zustände IV Zur Psychotherapie des A B *Ztschr f kl n Med 110* 701—7.1 (19 9)
5? QUARLES VAN UFFORD W J *Gen esk Gids 9* 29 (1951)
53 REICHMAN F Zur Psychopathologie des Asthma bronchiale *Med Klin 18* 1066—1068 (1922)
54 ROGERS A *Counsel ng and Psychotherapy* Houghton Mifflin Company Boston, New York
55 ROMER C KLEEMANN A Das Asthma und seine Behandlung *Dtsch A ch klin Med 155* 307—325 (1927)
56 ROSS N WILSON CH *Psychotherapy in Bronchial Asthma* From the P ychoanalytic Clinic for Training and Research Department of Psychiatry Columbia Univers ty New York
57 SALTER H H *Asthma Its Pathology and Treatment* London Churchill 24 27 28 (1866)
58 SCHULTZ I H *Das autogene Train g* Thieme Stuttgart 1955
59 — Die Psychotherap e des Asthma bronchiale *Dtsch med Wschr 54* 964—965 (19 8)
60 — Asthma als psychotherapeutisches Problem *Zbl inn Med 344* (1929)
61 — *Autogene Tra n g* 6 Lindauer Psychotherapie Woche 13 5 55 Thieme Leipzig (1956)
62 SCHWÖBEL G Psychosomatische Therapie des Asthma bronchiale *Är tl Fo sch 2* 481 (1948)
63 SIVADON P Psychologie du tra ail *L évolution psychiatrique 3* 451 (1952)
64 — Les clubs soc otherapiques à l hôpital psychiatrique *L A née méd co psychologiqu 1* 484 (1957)
65 — BAUME S Le club de post-cure de l elan *A née médico psychologique 1* 489 (1952)
66 SKANDS M C A case of asthma treated with psychotherapy *Am J M XI* 117 (1951)
67 STOKVIS B De Organpsychose (Meng) in ihrer Bedeutung fur die Psychosomatische Medizin *Psyche VI* Heft 3 (1952—1953)
68 — A paper read before the combined meeting of the Dutch Soc Psychiat and Neurol Utrecht 5 2 1954
69 — *Hypnose in der a ztlichen P a s* S Karger Basel—New York 1955
70 — *Psychosomatik d r Entspan ung* (in course of preparation)
71 — WELMAN A J Groeps en soc otherap e als adjuvans ter behandeling van lijders aan a thma bronchiale *Ned T v G 99* 693 (1955)
72 — — Psycho- en sociodrama als uitbeeldende psychotherapie bij pat ënten met psycho somatische aandoeningen *Ned T Geneesk 99* 1482 (1955)
73 TAGERBERG E The importance of Psychologic factors in Bronchial Asthma *Acta Allerg VI* 61—79 (1953)
74 THOROWGOOD J C *The Lettsom an Lectures on Bronchial Asthma* 12 1 Balliere Tindall and Cox London (1879)
75 TRAUTWEIN H Das autogene training in der Behandlung des Asthma bronchiale *Är tl Forsch 3* 489—492 (1949)
76 UNGER L GORDON B F *A n of All 7* 565
77 VAUGHAN W F *Pract ce of Allergy* Henry Kempton London
78 WEISS E Psychosomatic aspects of certain allergic disorders *I t A ch Allergy 1* 4 (1950)
79 ZOSS S R *Ann f All 7* 735

DISCUSSION

D LEIGH

In any consideration of the psychological aspects of asthma sound scientific methods must be used

A brief résumé of a statistical study of the psychiatric symptoms found in asthmatic patients with adequate control material reveals some interesting findings In order to avoid the criticism that asthmatics who attend a psychiatrist differ in some way from asthmatics who attend a general physician a control group of asthmatics attending a general physician was compared with a group of asthmatics attending a psychiatrist Two further control groups were used a group of neurotic patients and a group of normals

Using Student s t test it was possible to show that there was little significant difference between female asthmatics attending a general physician and those attending a psychiatrist There was a marked difference however in the male population Men who attended a psychiatrist were very much more disturbed psychiatrically than those attending the physician When compared with normals and neurotics the asthmatics were seen to fall somewhere between the two in their particular ratings

These findings are being extended and amplified as they have considerable theoretical interest both aetiologically and therapeutically The main purpose however of this brief communication is to put forward a plea for the use of sound statistical and scientific methods in the study of the psychological aspects of asthma

P J VAN DER WERFF

I do not agree with the view that psychosomatic medicine is a modern branch of science since it is as old as the history of mankind We realize this when we see the pictures in caves made by prehistoric men especially those in Spain or when we see read or hear about the medicine men of recently discovered primitive tribes in Western Australia Mid West Africa or the virginal forests of South America one of the differences in methods being that these witch doctors spoke and speak through wooden tubes and not on the radio such as sometimes occurs nowadays

The good general practitioner of to day who is the faithful friend of the family and the specialist who does not treat cases but human beings with somatic disturbances and diseases are also practising genuine psychosomatic therapy every day

Therefore apart from allergenic factors bacterial infections in the respiratory tract and elsewhere in the body endocrine disturbances etc and now only in regard to psychogenic factors what makes us allergists reluctant are several principles of certain psychosomatic work teams for we do not deny the importance of the psychological factors We hesitate to accept the principle of the specificity of the personality structure and of the specific conflict situations of psycho-

somatic patients in general and of patients with asthma in particular as we see all kinds of neurotic reactions mental disturbances and all kinds of personality structures in our patients with bronchial asthma as well as in those with colitis or with combinations of these and other allergic syndromes Although I cannot agree with their points of view on the other hand I do agree with the views I heard to-day from the mouth of Dr Stokvis as a representative of the Leyden School (although the problem of specificity has not been mentioned as it was beyond the scope of the program of this Round Table Friendship Meeting)

But still I should like to put two questions to Dr Stokvis

1) What is your opinion on the question of primary or secondary psycho genic asthma?
2) When you assume the existence of both i e a primary and a secondary psychogenic origin does this make any difference to your psychotherapy?

My questions are based on a case (which you perhaps remember yourself) of a man of about 45 no known allergies in the family with only a slight allergy to inhalants and foods He was unable to do any work due to a characteristic bronchial asthma He was 6 months old when his mother died he was brought up by an aunt shortly after he had his first attack of asthma Is it possible that here we were concerned with a patient as has been described by Alexander affected with a primary psychogenic asthma?

K WILKEN JENSEN

Unfortunately the paper of the relator was quite different from what I expected and it contained so many fine psychiatric expressions which I do not know that I cannot enter into any discussion with him

In spite of that I would like to mention that a few years ago a specialist in children s psychiatry a couple of psychologists and two allergologists made a rather intensive investigation of about 50 allergic children who were examined for their allergy as well as for their psychologic qualities As controls served a group of children with different behaviour disorders and a group of so called normal school children The results were published at the 10th Northern Paedia tric Congress in Stockholm but have only been printed as a summary I shall not go into details about the investigation the results of which were compared by means of cards with a system of holes The psychologic differences between the groups were only small especially between the allergic and the neurotic group the only difference of real importance being that the allergic children were more anxious and this anxiety may even be secondary to the asthmatic attacks so that the asthma has caused the anxiety A special psychologic type was absolutely not to be found in the allergic group

E WOLFER BIANCHI

In my opinion we are speaking nowadays too much of psychologic factors in the origin of asthma and the need of psychological treatment In several thousand cases of asthma the probable psychical origin was stated only in one patient

In a minimum of 20 cases in which I thought that psychological factors would impede the results of our treatment during the illness I sent the patients to a psychotherapeutic specialist This was always a failure Also I never saw a good result by hypnosis The asthma should not be called a psychosomatic disease it is a somatic one in clinical and anatomical view and should be treated with our clinical methods In each disease we find psychological troubles It is the task of the physician treating asthmatic patients to look after their psychical conditions and troubles and to help them by the simple methods of the so called short psycho-therapy

REPLIES

by

B STOKVIS and A J WELMAN

to J F Farrerons Có

We have had the same experience as Dr Farrerons

There is a certain risk of losing a patient who refuses to accept the suggestion of consulting a psychiatrist At our Center we dealt with this problem by inviting the internist personally to introduce the psychotherapist to the patient It is on the manner in which this first contact is established that the success or failure of the subsequent psychotherapy depends

to D Leigh

We should like to stress the fact that we quite agree with Dr Leigh in principle We tried to make it quite clear in our paper that control material (catamnestic examination) is indispensable for judging the results of the psychotherapy We have followed up our patients for periods between six months and three years For this reason we have discussed only thirty patients out of the eighty we have so far treated psychotherapeutically in our Center That is why we preferred to avoid any pseudo accuracy by not presenting statistical data Moreover we did make a comparison between the psychotherapeutic results in asthmatics (somato neurotics) and those in psycho neurotics We may conclude therefore that Dr Leigh s views and our own are in essence very similar

to E Wolfer Bianchi

We quite agree that in many cases the psychic component of the asthmatic trouble appears hardly perceptible We therefore invariably make at our Center in every case of asthma a psycho-diagnostic examination Only in this way one can reveal the actual presence of the psychic factor

to P J van der Werff

Yes we are in fact of the opinion that there exist both primary and secondary

psychogenic asthma although it is not always an easy matt r to decide which is which in a given case The somato-allergic determinants and the purely psychic ones are very often inextricably mixed up Moreover these factors influence each other mutually

Secondary psychogenic asthma is exceedingly frequent on account of the almost invariable neurotic way in which the patient experiences his state of chronic illness In addition there is the frequent action of some conditioned reflex even in those cases where the neurotic complication is not present

I wonder whether the case to which Dr Van der Werff refers was a case of primary psychogenic asthma with subsequent somatic allergy to inhalants and foodstuffs Of course we do not know anything of the earlier contact of the patient—when he was a baby—with allergenic factors e g house dust etc

In this respect Dr Welman and I want to emphasize that—in our opinion—psychosomatic factors should be distinguished into

1) psychic
2) somatic } factors
3) social

In our Center we always try to investigate these three factors together in every s parat case and we definitely give our full attention especially to the *somatic* allergenic factors Our psychosomatic therapy is determined by th se three factors and of course in many so-called psychogenic cases the somatic therapy is very important Let us never forget that all illnesses are multiconditionally determined We do not agree with the monocausative aetiological theory

With regard to Dr Van der Werff s second question the presence of either primary or secondary psychogenic asthma makes no difference to the therapy

I may perhap add that the Leyden Psychosomatic Center does not adhere to the principle of sp cificity with respect to the personality stru ture and conflict situations of psychosomatic patients in general and of asthma patients in particular

Dr Van der Werff s questions appear to me of essential importance because if my explanation is correct the bone of contention between allergologists and early psychiatrists thereby vanishes into thin air

to K Wilken Jensen

We are very pleased to note that Dr Wilken Jensen had the same experiences in making his very interesting psychological experiments as ourselves We should like to thank him for his statement to that effect

to R S Bruce Pearson

This is a very important question In psycho-therapy too we have our sharp indications and contra indications It is especially the patient s personality structure that determines the type of therapy to be applied Discovering psychotherapy needs sufficient intelligence and introspection on the patient s part Covering

methods (suggestion and auto suggestion) may be used in all cases Middle aged patients should be induced to resign themselves to accepting the fact of their illness For these patients analysis is contra indicated owing to the lack of integrative possibilities Whenever possible we give them some insight into their life s problems (short psychotherapy of Alexander and French) and failing this an (auto) suggestive or suggestive psychological treatment

BREATHING EXERCISES AND GENERAL GYMNASTICS IN PATIENTS WITH BRONCHIAL ASTHMA *

by

W J QUARLES VAN UFFORD

The dyspnoea associated with asthma is due to spasm of the smooth muscle tissue of the bronchioles obstruction of these air passages by viscid mucus or rapids welling of the mucosa In each of these three cases the result will be identical viz the alveolar air is expired with great difficulty This is due to the constriction of the respiratory tract in spiration but *especially expiration* has become difficult and this results in dilatation of the alveoli and depression of the diaphragma

All muscles are in action the normal muscles of respiration the accessory muscles of respiration of the shoulder neck and even those of the nose

In terms of physiology the residual volume has increased (e g to 40 per cent instead of the normal 25 per cent of the total lung capacity) the vital capacity (= tidal air + complemental air + supplemental air) has decreased and the so-called 1st second value has decreased By the term first second value we mean the percentage of vital capacity that can be expired in one second after an inspiration of maximum depth followed by an expiration of maximum depth and maximum speed

This percentage is also called the *utilizable portion of the vital capacity* as it shows what portion of the vital capacity can be utilized

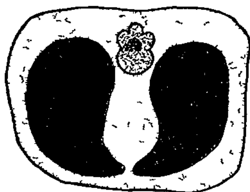
Bronchial asthma in which the expiratory phase is prolonged is marked by a diminished first second value Thus the percentage may be 50 per cent instead of the normal 70 per cent—85 per cent of vital capacity

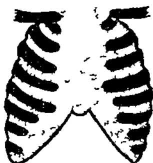
Pulmonary function tests following the injection of adrenaline show a considerable improvement of the respiratory curve This is of particular importance in determining the degree to which the changes in asthma are reversible

We shall examine the effect of attacks of dyspnoea on the body and the extent to which physical therapy may be used in *prevention* and *treatment* The great advantage of this method of treatment is that the patient is p ovided with a weapon which he can use at will We look with horror upon the abuse of pocket inhalers (of which the patient carries as many as 2 or 3 with him if possible)

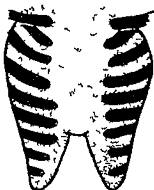
The purpose of postural and breathing therapy is not only to teach the patient what to do in case of emergency but also to improve and to prevent

* From the Allergic Department of the Diaconessenhuis Utrecht (Dir Dr M A. VAN MELLE)









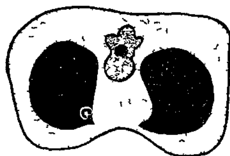




Fig 1

Fig 2

Let us imagine ourselves in the position of our asthmatic patient with chronic dyspnoea Let us give a moment s thought to his thoracic deformities his typical posture in which the chest moves rapidly up and down let us bear in mind his dyspnoea on any exertion his tense posture his anxiety

We shall examine what can be done on these fronts

1) correction of posture
2) breathing exercises
3) improvement of the resistance of the patient
4) relaxing exercises

Chronic asthma results in changes of the thorax the nature of these changes depending on the age of onset of the attacks of asthma (fig 1—7)

In infants the give takes place at the cartilages on each side of the sternum This bone is sucked inwards and may remain a deep con cavity throughout life

In children the chest assumes the pigeon breast type with the enlarge ment at the lower part of the chest not the upper

In older subjects the bone cage is fully hardened and worked by strong muscles the result being the formation of the barrel shaped chest and the production of emphysema

It is the object of breathing exercises and postural therapy

1) to prevent and possibly improve the anatomical changes caused by the attacks of bronchial asthma

We shall illustrate this statement by the following example When children are ordered to sit smartly in elementary schools in this country they have to sit with their arms folded in front of them on the school desk This position results in forward displacement of the shoulders As it is patients with asthma are conspicuous for their stooped drooping shoulders Accordingly this would be promoted by the position of the children at school if they were not ordered to fold their hands behind their backs when sitting smartly so that the shoulders are drawn backwards

This correction of posture is also obtained by swimming which also is an excellent form of breathing exercise

I do not believe that the question what exercises are most suitable for a patient Swedish gymnastics the French system the Mensendieck system or whatever they may be called is the most important feature (fig 8—9) We must picture to ourselves how deformities of the chest dependent on his age and symptoms will occur in a patient with asthma and examine the best method by which to treat these changes in this case

To a large extent this will also depend on the patient It is foolish to determine in advance that all patients should in all conditions be

treated in accordance with a fixed scheme of treatment The physician should first ask himself the question what changes may be expected to occur in the chest and therefore how to treat these changes in the first place Horizontal bars will be an excellent apparatus in some cases morning and evening exercises performed by the patient himself being the best method in other cases

2) The patient with chronic asthma will grow accustomed to that form of respiration which he uses in case of distress He will mainly use the accessory muscles of respiration The elevated chest type of breathing is observed Only a small portion of the lung volume is used in this form of respiration What are the requirements to be met by respiration in patients with asthma?

As in the case of treatment to correct the posture we should begin by asking ourselves the question what we think we can obtain by altering the type of breathing to which the patient has grown accustomed

(There also are people who claim that it is foolish to try to change the type of respiration in a patient as the body itself will undoubtedly have found the best way out during attacks of dyspnoea)

Why then should we try to alter his elevated chest respiration? Should we attempt to direct his breathing into normal channels?

The larger the area involved the larger the O_2 uptake, and therefore the less severe the dyspnoea will be Moreover as the air circulates more freely through the various air passages ventilation effectively removing particles of mucus etc will improve which reduces the risk of infection etc

The era of technical science has resulted in the use of electric procedures The muscles are stimulated by an electric apparatus which compels a type of artificially induced correct respiration which becomes a habit

The various types of breathing exercises can be discussed at great length or very briefly one may choose between thoracic respiration flank respiration costo abdominal respiration pure abdominal respiration (and a variety of intermediate forms)

I do not wish to include the manner of working of the diaphragma abdominal muscles and thoracic muscles and what type of synergy results in a particular form of respiration within the scope of this discussion

One of the most valuable exercises consists in practising prolonged expiration The patient is given a watch (with a seconds hand) or a stop watch is ordered to inspire deeply and then to expire deeply and as slowly as possible

This exercise offers the advantage that the patient is able to verify the result obtained and is able to see what improvement he has made



Fig 3



Fig 4



Fig 5



Fig 6



Fig 7

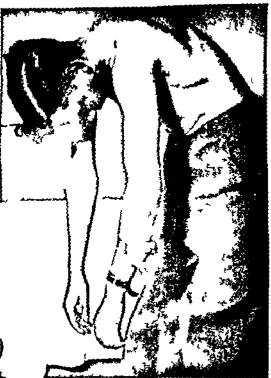

Fig 8


Fig 9

Fig 10

Fig 11

This method also serves to clear the chest completely Accordingly the exercises initially frequently result in fits of coughing accompanied by the expectoration of viscid sputum Another exercise the results of which can be readily verified by the patient is that in which a tape measure is employed (a leather band or belt may also be used) In our department of physical therapy we proceed on the assumption that the average patient must be able to achieve a difference of at least 10 cm between in and expiration The tape measure is applied around the lower part of the thorax This method often results in a marked improvement in respiration It obviously promotes flank respiration during which the abdominal muscles remain tense

In our opinion pure abdominal respiration during which the abdomen projects like a balloon to be subsequently drawn in again has the considerable drawback, that ventilation (and therefore the removal of sputum) is not sufficiently stimulated as this types of breathing chiefly affects the caudal portions of the lung

Although I have been aided by an assistant trained in Cesar s method of kinesitherapy (fig 10—11) in my own practice both in the hospital and in the out patients department for about 8 years I continue to be convinced that he or she who tries to help the patient devotedly with all the power at his command will obtain results whether he belongs to an orthodox school uses Cesar s method Mensendieck s system Yogi therapy or any other method of treatment The primary question is in what respect the breathing technique of the patient is deficient and by what method it can be improved

So far our knowledges has not advanced sufficiently to enable us to definitely prefer one system to another What is important however is the enthusiasm and perseverance of the instructor and the patient s persistence in performing the exercises himself Nothing will be achieved by 5 minutes or even 30 minutes a day The patient must understand what the instructor wishes to accomplish and be shown the road to this goal

The personal system used in the treatment of our patients is

a) the hospitalized patient must frequently see to female instructress the more he practises the better (the risk of *too much exercising* need not be considered)

b) after examination all the out patients are given instructions to which other instructions are added in course of time Now and then the results are checked and discussed with the patients

c) in the case of children and patients with chronic asthma exercises are performed once or twice weekly if possible for several years

In this connection I wish to take a stand against two views the first being that treatment of children with so-called medical

gymnastics is a matter of months Asthma therapy is a treatment of chronic patients which is bound to involve a considerable period of time This is also true of medical gymnastics In these days when allotments often have to be granted through the intermediary of medical officers employed by insurance companies it is advisable to fully realize that the medical gymnastics instructor need not even begin treatment when the patient and medical officer are not both inclined to persevere

Secondly that physical therapy is useful only in children From the preventive and curative point of view physical therapy is of importance in every case of chronic or frequently recurring asthma and striking results can even be obtained in a large number of chronic patients with a prolonged history of asthma When we have exercised extensively with a patient with emphysema and a striking result has been obtained both in his opinion and ours another pulmonary function test shows *the reserve to be the case only a subjective improvement* has been obtained nevertheless the performance of the patient will have increased considerably

3) Exercises combined with movements

A patient with chronic asthma was hospitalized for persistent dyspnoea in the daytime as well as at night On hospitalization he was given medical treatment which reduced the dyspnoea until treatment could be discontinued

Among other things we started performing breathing exercises To my remark so you see that you can be free of symptoms he replied just wait until I am allowed up He was allowed up just you see and wait until I m allowed in the corridor He was allowed in the corridor just wait and see until I m allowed out of doors He went into the garden just wait and see until I go about in the streets This game was constantly repeated until he was able to take 3 hour walks In the beginning he was accompanied by the instructor During his movements his attention was continually directed toward breathing errors Mentally he was helped to overcome his anxiety Somatically he was helped by obtaining a much better breathing technique In studying the history of a large number of patients with asthma we are struck by the fact how often the patient states that his attacks of dyspnoea alternate with intervals marked by the absence of coughing and wheezing except for laboured breathing shortness of breath a sense of constriction and even a slight dyspnoea after exercise

The child stops playing or romping sooner than others the adult is careful in running going up and down the stairs etc The patient is just in balance in the resting state but exercise results in dyspnoea (oxygen deficiency) As yet no emphysema has developed however A well known story which you can often hear tell is that of the patient with

asthma who is just able to catch a train starts running has severe dyspnoea continues running and in a manner of speaking runs through his dyspnoea

A similar story may be told by certain patients with vasomotor rhinitis whose nasal symptoms disappear on effort

I have mentioned the case of the patient with emphysema who showed a marked subjective improvement and a much better performance after vigorous breathing exercises but failed to show any objective improvement He has at least learnt to make a better use of the respiratory volume allowed him

The asthmatic patient with chronic bronchitis and slight bronchiectases who expectorates large quantities of mucus, will be grateful for the vigorous breathing exercises He still has to eject his mucus but he is at last relieved of his distressing cough reflexes and some viscid mucus Expectoration and therefore motion is considerably facilitated Although we personally are convinced that flank breathing is the ideal type of respiration in cases of asthma and can be kept up during movements I am quite open to other opinions

The chief feature is the patience observed in exercising the patient Actually I regard this as a form of training there are many systems for running rowing swimming etc some day one system may perhaps prove to be greatly preferable to all others but so far one can only say that excellent results may be obtained by all systems provided one perseveres in one s efforts As a rule the increased performance is not due to the system of training but to its persistent and vigorous use

Our respiratory volume is completely sufficient when you or I have to walk slowly for 100 metres it is also sufficient to climb the first stairs in houses on the Amsterdam grachten but which of us arrives easily at the finish when we have to run 100 metres or climb the fourth staircase? Thanks to their training and increased performance, i e a better use of the body and respiratory volume the runner and the Amsterdam doctor and milkman do indeed succeed in doing so

The same applies to our patients with chronic asthma who are in balance when walking slowly but lose their balance when running They also have to be trained They must learn again to increase the respiratory volume granted to them if possible and at any rate to use it well and to perform the best possible movements In treating these patients the physician will keep asking himself how he can again increase the respiratory volume

It is by no means sufficient to teach the patient to breathe correctly in bed or in his chair

He must also be able to do something with his improved breathing technique

For the time being those patients who also are often short of breath indoors will be grateful for this result Patients whose only symptom during the intervals consists in dyspnoea after exercise will undoubtedly be more exacting in their demands however

4) Finally there is an entirely different form of exercise relaxation therapy Uttering these words immediately calls to my mind certain patients in whom everything seems to be spasmodic They are often liable to dyspnoea but their entire appearance gives the same impression It are these cases in which the first thing to do is to consult a psychiatrist But even then there still remains that state of dyspnoea of convulsiveness in their asthma and throughout their body

We first start giving these patients relaxation therapy (beginning with the phrase speak to your muscles the patient lying at his ease being taught to consciously relax the muscles in every part of his body) I got acquainted with this form of therapy in the Physiotherapeutic Department of the Brompton Hospital (London) It undoubtedly affords relief to a number of patients

Having been quietly taught how to relax their muscles the tendency of the bronchial muscles to spasms will also decrease I imagine the dyspnoea diminishes, the sense of constriction disappears This result is indeed sometimes obtained by the doctor visiting the patient in bed by a quiet talk with the nurse which takes the patient s mind off his condition and even by going to the hospital when this general spasmodic state disappears the despair will also decrease spontaneously

Undoubtedly not every attack of asthma can be controlled by relaxation of the muscles and nervous as well as mental relaxation Acute severe dyspnoea fails to respond to words spoken to the patient

The patient cannot and does not wish to lie down in a relaxed state in that case a physiologic saline solution administered as if it were the best possible drug will certainly be of no avail the patient looks at you expectantly and finds that his dyspnoea fails to decrease

It are these cases, marked by constant dyspnoea agitation and wheezing that show a favourable response to relaxation therapy

Also it usually are these cases which are cited to illustrate the fact that breathing exercises and relaxation therapy are a form of psychotherapy

We must picture the various forms of dyspnoea to ourselves

acute severe dyspnoea true status asthmaticus cannot be prevented or treated with breathing exercises or relaxation therapy Here we are concerned with that form of dyspnoea in which the patient develops severe symptoms feels as if his breath were cut off and has a sense of constriction the forms of chronic dyspnoea marked by unproductive cough and a wheezing breath and especially those forms of chronic dyspnoea of a marked general spasmodic character which do respond to treatment

In addition we are concerned with *prevention* prevention of the sequelae of the chronic disease The warning uttered by Unger in his book is also applicable in this case Both statistical reports published by physiotherapeutists and reports on clinical cases are often characterized by the proud statement that excellent results have been obtained even when no additional antiallergic treatment was given

But it is impossible to report statistical data showing that treatment was completely successful in all cases

Why not co operate? Why should physical therapy not be regarded as a highly valuable adjunct? Does not a fractured bone first have to be set and heal completely before the physiotherapeutist is able to restore movements involving the use of this bone? Attacks of asthma really are not due to a poor breathing technique many individuals have an equally poor breathing technique, but nevertheless they do not wheeze

The same is true of asthma Certain conditions associated with asthma are treated certain sequelae of asthma are prevented but there is no successful treatment of asthma and even the next genuine attack is not prevented

Finally I wish to add some words concerning other possibilities in the same field The cheapest and yet a very good form of breathing exercise and correction of posture is swimming Moreover the psychologist will be able to tell you how important it is to experience the sensation of the light body floating in the water A similar sensation is experienced in ballet dancing when the feeling of gliding over the dance floor induces a beautiful and valuable sense of body control Breathing exercises are essential to good singing But on the other hand are not the drawn out tones in singing excellent expiration exercises? Especially in young children these forms of singing dancing and exercise during the performance of fairy tales often are effective in attaining the end desired

SUMMARY

The purpose of physical therapy is

a) the prevention or correction of changes in posture and deformities

b) improvement of the type of breathing

c) to increase the power of endurance while retaining the correct breathing technique during movements

d) relaxation therapy

Various forms of chronic asthma respond very favourably to this treatment

Literature

ABRAMSON H A *Somatic and psychiatric treatment of asthma* Baltimore Williams and Wilkins 1951

ASTHMA RESEARCH COUNCIL. *Physical exercises for asthma* London 1946

ANGROVE H S *Remedial exercises for certain diseases of the heart and lungs* London Faber 1948

BAKER FRANCES Exercise in the treatment of asthma *Archives of Physical Med vol XXXII* 30—33 1951

BARACH A S *Physiologic therapy in respiratory diseases* Philadelphia Lippincott 1948

BELINFANTE DEKKER M *Hoe gen es ik zelf asthma en bronchitis* A dam Wereldvenster 1951

DERBES V J ENGELHARDT H T *The treatment of bronchial asthma* Philadelphia Lippincott 1946

DORINSON S M Breathing Exercises for Bronchial Asthma and Pulmonary Emphysema *J A M A* 156 10 931 1954

DRINKER C K *The clinical physiology of the lungs* Springfield Thomas 1954

FEIN B T COX E P GREEN L H Respiratory and Physical Exercise in the Treatment of Bronchial Asthma *Annals of All* 11 3 275 1953

FINK D H *Release from nervous tensions* London Allen and Unwin 1952

GAY L N *The diagnosis and treatment of bronchial asthma* Baltimore Williams and Wilkins 1946

GARDENER M DENA *The principles of exercise therapy* London Bell 1954

HERNANDEZ M Muscular Exertion and Eosinophils *J A M A Foreign Letters* 155 17 1519 1954

HOFBAUER L *Asthma* Wien Springer 1928

HIRSCHEIMER H G J *Management of bronchial asthma* London Butherworth, 1952

KOFLER R *Di Kunst des Atmens* Leipzig Breitkopf und Härtel 1914

KLEWITZ F *Das Bronchial Asthma* Dresden Steinkopff 1928

PARON J *Funktionelle Atmungstherapie* Stuttgart Thieme 1953

PHYSIO THERAPEUTIC DEPARTMENT BROMPTON HOSPITAL, LONDON *Instructions asthma and bronchitis breathing exercises*

RAMACHAROKA *De Yogi wetenschap der ademhaling* Amersfoort Veen 1954

ROSSIER P H PIPBERGER H MEILI E KÄLIN R Zwerchfell und Asthma *Schwei m d Wchnschr* 83 45 1095 1953

SAMBUCHY A M *de Asthme à l Espalier* Paris Legrand 195?

SCHUTZ K A theoretical modern explanation of the favourable action of breathing exercises stress *New York J Med* 55 635—643 1955

TIDY N M *Massage and Remedial Exercises* Bristol Wright 1947

UNGER *Bronchial Asthma* Springfield Baltimore Thoma 1945

URBARCH E GOTTLIEB PH M *Allergy* New York, Grune and Stratton 589—600 1949

WINDEMÜLLER PH J *Over grenzen en mogelykheden van de spirografie* Ac Utrecht 1951

WALKER G F *The asthmatic Child* Bristol Wright 1950

WYSS F *Asthma bronchiale* Stuttgart Thieme 1955

DISCUSSION

K H BAAGOE

Just a few words about abdominal breathing in the treatment of asthmatic patients

First I want to mention that I know and have used though only for a short time two systems of exercises the British Physical Exercises for Asthma published by Asthma Research Council (1935) and the Danish system originated by Hans Heckscher (1946)

However when I have not used these two systems to any greater extent it is chiefly because nearly all my patients are dealt with in a consulting practice and come from far away and must be finished with in one consultation

So in recent years I have confined myself to teaching my patients two exercises which can be learned by most patients in a few minutes and the principal aim of which is to make the patients breathe abdominally secondarily they are exercises in relaxation

Besides by confining the exercises to abdominal breathing I have thought that I should be able to g t information about the importance that one can ascribe to this form of breathing which forms part of the various respiratory systems

The one is taken from Heckschers exercises In this the patient with the flexed knees and hips bends forward with the head resting on the hands in a completely relaxed position If the patient now lies completely relaxed abdominal breathing takes place spontaneously

The second exercise is number one in the British system and consists in the patient lying back with knees drawn up and one hand placed on the belly to make sure that the breathing is done with the abdomen

Nearly all patients can learn these excercises in a single consultation I have only told them to breathe with the abdomen and not instructed them to breathe particularly deeply

If the patients can perform these two exercises without difficulty at the first consultation which shows that they have control of their respiratory muscles I show them too that they can also easily breathe abdominally in a sitting position with the body bend forward and the elbows resting on the knees and that they can do it in a standing position as well

I do not know how many of my patients continue these exercises after getting home I can only state that the majority of the patients who have consulted me again have performed the excercises at home and have stated that the exercises helped them

The effect of the abdominal breathing is best illustrated by some examples

1) A young girl of 23 had for 5 years been suffering periodically from mild asthmatic attacks When she first consulted me I found ronchi over both lungs but borders of the lungs normal When 3 months later she consulted me again she stated that she no longer used any medicine but that she could abort her asthmatic attacks exclusively by breathing abdominally For the present she had

a cold she said At the examination no ronchi were heard and when I told her this she exclaimed Oh I can easily manage to wheeze and while she had hitherto breathed abdominally as I had taught her she now took a few deep breaths with the thorax with the result, that ronchi were heard over both lungs

My first thought was that the cause of the wheezing was that she breathed more deeply when respiring with the chest So I asked her the next time she had an attack of asthma to try to breathe with the chest but not so deeply and see whether she could abort the attack in this way

Some time after I got a letter from her in which she told me that she had made the attempt but had failed For if she tried to breathe so little with the chest that the wheezing stopped she could not get sufficient air so that she soon had to start breathing abdominally—with the usual good result

2) A 31 year old working man with asthma told me that if he took a few abdominal breaths now and then he could take his midday rest lying on his back which he had not been able to do before He also did these exercises at night after he had gone to bed as he felt that he got more air into the lungs in this way and consequently slept better

3) Another patient a labourer of 62 who besides asthma had clinical emphysema was very unwilling and sulky when I showed him these exercises So I was greatly surprised when during a consultation 6 months later he told me that he did the exercises every evening and the most remarkable thing was that he stated that he could make wheezing caused by cycling against the wind stop by breathing abdominally while still cycling in the same way he could stop wheezing when he carried heavy weights

All together the statements of the patients agree They say that they have the feeling that they get more air into the lungs by abdominal breathing and that they can stop mild attacks and a few say that they expectorate more easily

However I have not found any lasting improvement of the asthma It is only a symptomatic remedy but one which the patient has at hand and which is useful whether he has emphysema or not I consider it an important supplement in the treatment of asthma in a consulting practise

Concerning the cause of the good effect one might think it was a psychic one owing to the patients attention being diverted from the attack This hypothesis is not supported by the case mentioned above in which the patient could make wheezing come and go at will Further one might think that the breathing was less deep in abdominal respiration but this does not seem to be the case in the patient mentioned above nor has a spirometric examination shown any difference in ventilation during abdominal and thoracic respiration in these patients

According to Wyss s demonstration of the importance of the diaphragmatic spasm in the asthmatic attack it seems to be most probable that it is the conscious abdominal respiration that can overcome a mild diaphragmatic spasm

LE TRAITEMENT DE L ASTHME PAR LA CORTICOTHÉRAPIE D APRÈS 95 OBSERVATIONS

par

PASTEUR VALLERY RADOT CL LAROCHE ET GILLES LYON

Nous rapporterons ici les resultats obtenus chez 95 malades atteints d asthme severe que nous avons traites depuis 1950

Tous ces malades ont ete suivis pendant plus de trois mois et 65 ont ete suivis pendant un à cinq ans Lorsque le traitement fut entrepris il existait un etat de mal asthmatique dyspnee permanente depuis plusieurs jours ou plusieurs semaines sur laquelle se greffaient des accès paroxystiques Certains malades étaient cyanoses et presentaient une tachycardie et meme dans 5 cas des signes d insuffisance ventriculaire droite

Voici comment se décompose la statistique de nos 95 malades

1° 58 malades ont reçu un seul traitement hormonal ACTH dans 36 cas cortisone dans 21 cas hydrocortisone dans 1 cas

2° 21 malades à la suite de rechutes ont dû subir plusieurs cures successives

10 d entre eux ont eu deux cures successives
- deux cures d ACTH dans 4 cas
- une cure d ACTH puis une cure de cortisone dans 5 cas
- une cure d ACTH puis une cure d hydrocortisone dans 1 cas

8 ont eu trois cures successives
- trois cures d ACTH dans 4 cas
- deux cures d ACTH et une cure de cortisone dans 3 cas
- deux cures d ACTH et une cure d hydrocortisone dans 1 cas

2 ont eu quatre cures successives d ACTH dans 1 cas de cortisone dans l autre

1 a reçu en quatre ans 22 cures successives soit une cure environ tous les deux mois L ACTH et la cortisone ont éte alternees

Ainsi nous avons pratique chez ces 21 malades 48 cures d ACTH 24 cures de cortisone 2 cures d hydrocortisone

3° 16 malades ont reçu des traitements prolongés sans interruption pendant plus de trois mois nous étudierons plus loin les problèmes que pose cette methode

Si l on excepte les traitements prolonges chaque cure d ACTH

ou de cortisone a duré en moyenne dix à quinze jours elle a été plus longue lorsque apres ce laps de temps l auscultation révelait la persistance de sibilances dans les champs pulmonaires ou lorsque le sujet presentait encore de légeres crises ou une dyspnée a l effort Nous avons ete ainsi amenes dans certains cas à poursuivre le traitement hormonal pendant vingt à trente jours en abaissant progressivement les doses

Posologie

L A C T H etait injectee par *voie intramusculaire* a raison d une injection toutes les six heures pour les doses d attaque Au dessous de 100 mgr par jour, nous espacions les injections toutes les huit ou douze heures

Le fractionnement des doses est indispensable étant donne la courte duree d action du produit

Nous avons fait parfois des *perfusions* d A C T H par voie veineuse en injectant lentement en six à huit heures de très faibles quantites d A C T H (10 à 20 mgr par jour) dissout dans 500 cc de serum glucose Ces perfusions ont l inconvenient de nécessiter une surveillance très étroite du malade et en particulier de sa pression arterielle pendant toute la duree de l injection cependant chez nos malades nous n avons jamais observé d elevation tensionnelle notable

Si avec la perfusion la sedation de la dyspnee a eté parfois tres rapide s effectuant dès la quatrieme heure l efficacite de cette methode ne nous a pas paru superieure a celle des injections intramusculaires

Nous avons injecte dans quelques cas l A C T H par la *voie intradermique* mais les resultats ont eté très inconstants Très bien supportees chez certains malades les injections intradermiques ont provoqué chez d autres des réactions locales douloureuses et l hormone n a pas eu ses effets habituels du fait de la mauvaise resorption du produit

Nous avons récemment employe dans 2 cas une solution d A C T H *retard* cette solution est a recommander dans les traitements de longue duree car elle permet de limiter les injections et de diminuer la dose de l hormone Cependant dans les états de mal ou l on veut obtenir une action rapide, il est préférable d utiliser les solutions ordinaires

La *cortisone* a eté administree chez nos premiers malades par la voie intramusculaire nous avons ensuite utilisé exclusivement la voie gastrique qui nous a donne des resultats aussi satisfaisants Elle ne fait pas courir le risque d une infection aux points d injection La rapidite d action quand on utilise la voie gastrique serait meme augmentée si l on en juge par la chute des eosinophiles du sang et par la disparition des symptomes cliniques

Pour le traitement d attaque la dose quotidienne de cortisone etait

divisee en quatre à six prises reparties egalement dans les 24 heures Les prises etaient espacees quand à la fin du traitement les doses etaient diminuées

Le fractionnement des doses est encore plus important pour *l hydro cortisone* que pour la cortisone car la duree d action de l hydrocortisone de depasse guère six heures

Quelle que soit l hormone utilisee les doses doivent toujours etre fortes d emblee puis progressivement degressives

Pour l A C T H les doses d attaque ont varie entre 100 et 150 mgr par jour en quatre injections Ces doses etaient continuees pendant trois a huit jours puis abaissees graduellement

Il ne faut pas abaisser les doses d A C T H trop vite il faut s efforcer d obtenir une disparition totale non seulement de la dyspnee et de la toux mais des sibilances pulmonaires sinon la rechute est toujours rapide Cette action complète de l hormone ne s observe guere avant le huitième jour on ne doit donc pas donner une dose inferieure a 75 mgr avant le huitième ou le dixième jour On peut terminer la cure par de faibles doses (50 puis 25 mgr) destinees plus à eviter un sevrage hormonal brutal et une insuffisance surrenale secondaire qu à agir directement sur l etat asthmatique La cure dure donc en moyenne dix à quinze jours avec un total de 700 a 1 500 mgr d A C T H ce chiffre etant très variable selon les sujets

Il n y a aucun rapport entre la dose totale d A C T H et la remission Il est donc inutile de prolonger la cure

Si apres les quarante huit premières heures de traitement on n a pas obtenu d amelioration on peut elever les doses à 200 mgr par our par exemple il n est pas rare d observer ainsi une action favorable en effet il semble exister pour chaque patient une dose seuil au dessous de laquelle l A C T H est inactive

Si l etat de mal persiste apres trois ou quatre jours malgre des doses elevées d A C T H il faut essayer une autre hormone de preference l hydrocortisone

Les traitements avec la *cortisone* et avec *l hydrocortisone* sont regis par les memes règles que celles que nous venons d enoncer pour l A C T H

La dose initiale doit etre assez elevee entre 150 et 200 mgr par jour pour la cortisone 100 à 125 mgr pour l hydrocortisone Ces doses sont poursuivies pendant trois à huit jours puis abaissees progressivement afin d eviter les accidents de sevrage hormonal

La dose totale de cortisone est d ordinaire un peu plus eleveeq ue pour l A C T H et se situe entre 1 000 et 2 000 mgr administres en dix à quinze jours

Les doses d hydrocortisone sont d habitude de 30 p 100 inferieures a celles de la cortisone

Faut il faire suivre les cures d A C T H par quelques prises de cortisone ou d hydrocortisone et, reciproquement, les cures de cortisone ou d hydrocortisone par quelques injections d A C T H ? Cette technique a ete proposee par certains auteurs pour prévenir une insuffisance surré nale Elle ne nous a pas paru particulierement utile Il ne semble pas que l on puisse redouter un epuisement des surrenales par l A C T H ou une insuffisance surrenale transitoire apres la cure de cortisone

Pesultats

Les resultats obtenus avec l A C T H la cortisone ou l hydrocortisone varient beaucoup suivant que l on considère les resultats immediats ou la duree de rémission de l asthme apres la fin de la cure

Ces trois hormones nous ont permis d obtenir une sédation plus ou moins rapide des symptomes fonctionnels chez 80 malades Nous avons eu 15 echecs parmi lesquels certains malades ont ressenti une legere amelioration de la dyspnee mais avec persistance d un essoufflement permanent et de paroxysmes encore pénibles en particulier nocturnes Parmi ces 15 échecs il y eut 4 morts dans le classique tableau d asphyxie et l autopsie a revele les lesions habituelles de l etat de mal asthmatique caractérisees par un encombrement très marqué des bronches

Dans les cas favorables l action du traitement s est manifestee d ordinaire dans les vingt quatre premieres heures par une atténuation progressive de la dyspnee et de la cyanose et par la diminution de violence des accès paroxystiques les malades ressentaient un soulagement remarquable et retrouvaient le sommeil Il persistait encore pen dant deux à trois jours des petites crises dyspnéiques ainsi qu une recrudescence de l essoufflement au moindre effort L expectoration diminuait souvent et meme pouvait disparaitre completement cet assechement s explique par la disparition de l oedème de la muqueuse bronchique sous l effet des hormones la bronchoscopie montre un affaissement de la muqueuse qui reprend une coloration normale Cependant dans certains cas la bronchorrhée pouvait etre encore assez abondante pendant quelques jours mais prenait un aspect muqueux et fluide Les cellules éosinophiles disparaissaient de l expectoration très souvent dès le deuxieme jour du traitement

Les sibilances pulmonaires persistaient encore quelques jours apres la sedation de la dyspnee

L action immediate de la corticotherapie sur l etat de mal asthmatique est donc souvent tres remarquable *Les résultats à distance* sont beau coup moins brillants Voici les resultats

Dix asthmatiques ont beneficie de la corticotherapie pendant un laps de temps superieur a six mois des crises assez severes ont reapparu chez l un d eux au bout de six mois chez 2 autres au bout d un an chez 2 autres au bout de deux ans 5 autres n avaient pas encore eu de rechutes de l etat de mal après six mois (1 cas) apres deux ans (1 cas) après quatre ans (2 cas) apres cinq ans (1 cas)

Chez 5 malades la duree de la rémission n a pas dépasse trois a six mois

Chez 14 autres la remission ne fut que de un a trois mois

Tous ces sujets avaient ete liberes completement de leur asthme à la fin du traitement Certains conservaient une legère dyspnee d effort ou voyaient reapparaitre quelques crises dyspneiques facilement combat tues par les therapeutiques habituelles mais ils avaient repris une vie normale

Dans 26 cas la rechute s est produite moins d un mois apres l arret du traitement et dans 18 cas des l arret de celui ci

Dans 7 cas nous n avons pu savoir la duree de la rémission

Peut on prevoir l effet du traitement? Il semble que non Que l asthme soit allergique ou du a une surinfection bronchique qu il soit severe ou non qu il soit recent ou ancien que le sujet soit jeune ou age les resultats sont imprevisibles

La reprise de l etat de mal nous a amenes à pratiquer *plusieurs traite ments hormonaux successifs* (dont nous avons donne plus haut le detail)

Ces cures successives nous ont permis de *comparer* chez les memes malades *l efficacite* de l A C T H de la cortisone et de l hydrocortisone

Nous n avons pas note de difference sensible entre les effets de l A C T H et ceux de la cortisone ces deux hormones donnent d ordi naire des resultats identiques lorsqu elles sont utilisees chez le meme malade La cortisone administree par voie buccale et à doses assez élevees (plus de 100 mgr par jour) a une action aussi rapide que l A C T H et la qualite de l amelioration immediate de meme que la durée de la remission ne varient guere avec le produit employe Nean moins certains sujets reagissent mieux a l une des hormones qu a l autre

On pouvait penser que la mesure de la reponse surrénalienne a l incitation corticotrope par le test de Thorn permettrait de prevoir le degré d efficacite de l A C T H Comme nous l avons écrit dans un article précedent [1] nous n avons pu observer aucun parallelisme entre

[1] PASTEUR VALLERY RADOT LAROCHE CL MILLIEZ P DOMART A et RENIER J-C L A.C T H et la cortisone dans le tra tement de l état de mal asthmatique *Bull et Mém Soc méd d s Hôp* Paris 68 319 195.

la chute de l eosinophilie et l action therapeutique Des malades pre sentant des tests negatifs ont ete très améliores par l A C T H tandis que des echecs coincidaient avec des tests positifs On sait d ailleurs que la valeur du test de Thorn est tres relative chez les sujets presentant une eosinophilie sanguine elevee

Nous n avons de l hydrocortisone qu une experience trop recente pour etablir une comparaison valable avec les deux autres hormones Neanmoins nos premieres constatations ont ete très satisfaisantes puisque sur 10 cures d hydrocortisone nous n avons pas observe d echec Bien plus nous avons eu de bons resultats chez 5 malades qui n avaient pas ete ameliores par l A C T H ou la cortisone Il semble donc que l hydrocortisone possede une efficacite au moins egale et peut etre superieure a celle des deux hormones precédentes

Un certain nombre d auteurs pensent que chez les sujets soumis a des cures multiples d A C T H ou de cortisone ces hormones perdent une partie de leur efficacite Nos constatations ont ete differentes des cures hormonales successives nous ont donne des resultats assez con cordants

Malgré le danger de la *corticothérapie prolongee* nous avons ete amenes à faire chez 16 sujets des traitements continus [1] Il s agit d asthmatiques dont la dyspnee avait cédé sous l effet du traitement hormonal mais reapparaissait dès la fin du traitement

Nos premiers malades ont reçu de l A C T H mais nous utilisons actuellement plus volontiers la cortisone ou l hydrocortisone dont le mode d administration par voie buccale est plus simple

La *durée des cures* a ete variable de deux mois a trois ans

Quatre malades ont ete traités pendant plus d un an avec d excellents resultats L un d eux fait depuis trois ans des cures alternees de corti sone et d A C T H a des doses variant entre 50 et 100 mgr par jour Un deuxième a obtenu par la meme méthode un soulagement complet pendant deux ans puis a ete perdu de vue nous avons appris qu il etait mort recemment d un accident vasculaire independant de son asthme Un troisième prend sans interruption 75 mgr de cortisone depuis un an Le quatrieme soumis d abord à une cure continue de cortisone (75 mgr par jour) pendant trois ans prend actuellement depuis trois mois 10 mgr d hydrocortisone six jours par semaine

Huit autres malades ont ete traites pendant deux a trois mois avec des remissions totales par l hydrocortisone (3 cas) l A C T H (1 cas) des cures successives de cortisone et d hydrocortisone (1 cas) d A C T H

[1] Certains ont été suivis par le Dr B HALPERN

et de cortisone (2 cas) ou des trois hormones (1 cas) La corticotherapie a pu etre arretee chez 2 d entre eux apres deux mois sans qu il apparut de rechute Les 6 autres restent soumis au traitement hormonal qui ne peut etre interrompu sans une reprise immediate de la dyspnee

Sur 16 malades nous n avons eu que 3 echecs et 1 resultat mediocre Les 12 autres malades conservent la plupart un leger essoufflement à l effort et quelques rales sibilants mais ils menent une vie normale ils ne souffrent plus de dyspnée permanente ni d acces asthmatiques paroxystiques

La dose seuil au dessous de laquelle reapparaissent des symptomes fonctionnels genants est situee suivant les sujets entre 50 et 100 mgr d A C T H ou de cortisone par jour Elle varie d ailleurs chez un meme sujet et peut s elever sous l influence de certains facteurs tels qu une infection respiratoire Les malades règlent eux memes leur traitement au bout de quelques mois en utilisant la dose minimum active

Dans certains cas l action de la cortisone semble s epuiser mais des injections d A C T H pendant quelques jours semblent rendre le sujet de nouveau sensible a l hormone surrenale

Turiaf [1] pense qu il est preferable de n administrer la cortisone et l hydrocortisone que cinq jours par semaine mais l interruption de deux jours est parfois suffisante pour amener une reprise de la dyspnee

Bickernan et Barach [2] ont essaye de donner une dose forte de cortisone (400 mgr) un jour par semaine mais les resultats ont ete très decevants

La dose efficace d hydrocortisone est plus faible que celle de cortisone Turiaf la situe entre 30 et 40 mgr par jour

Nous avons employe recemment l A C T H retard avec succes chez 2 malades l un reçoit chaque jour une injection de 40 mgr de cette solution la dose d A C T H a ete ainsi reduite chez lui des deux tiers Chez l autre malade 40 mgr d A C T H retard donnent le meme resultat que 75 à 100 mgr d A C T H ordinaire et seraient plus efficaces que 100 mgr de cortisone ou 80 mgr d hydrocortisone

Nous pensons qu il est utile d intercaler pendant les cures prolongees de cortisone ou d hydrocortisone quelques injections d A C T H , toutes les quatre a six semaines afin de stimuler les cortico-surrenales et d eviter leur aplasie

TURIAF J MASLAND P et JEANJEAN Y Le traitement au long cours des asthmes à dyspnée continue par l'hydrocort sone en comprimés *Revue des Prat ciens 4* 1954 3037 3040

BICKERMAN H et BARACH A. Comparative results of the cure of ACTH cortisone and hydrocortisone in the treatment of intractable bronchial asthma and pulmonary emphysema *(J Allergy) 25* 312 3 4 1954

Precautions a prendre pour éviter accidents et incidents

L A C T H la cortisone et l hydrocortisone sont des corps dont l utilisation n est pas depourvue de danger Ils ne doivent etre employes qu à bon escient dans des asthmes graves ou les thérapeutiques usuelles ont echoue Cette restriction que nous avions formulee dès 1952 nous parait conserver toute sa valeur

Nous avons systematiquement soumis nos asthmatiques pendant le traitement à un régime sans sel Nous leur avons donné quotidiennement 1 a 2 gr de chlorure de potassium et nous leur avons fait prendre un antibiotique (d ordinaire tifomycine ou terramycine)

Nous n avons jamais noté d accidents oedémateux ou hypertensifs Les augmentations de poids ont ete faibles et n ont guere depasse 2 à 3 kilos encore faut il souligner que les grands asthmatiques sont souvent dénutris et que cette elevation de poids coincide avec une reapparition de l appétit elle ne peut donc pas etre attribuée dans tous les cas à la seule retention hydrosodique

L hydrocortisone entraine souvent apres quelques jours une augmentation de la diurèse qui peut etre passagère ou persister pendant toute la cure aussi les malades soumis à cette hormone présentent ils assez souvent une légere perte de poids Il n y a donc peut etre pas lieu de craindre ici la retention sodique et ce serait un des avantages de l hydrocortisone

L arret du traitement hormonal est parfois suivi d hypotension moderee et d asthénie cette insuffisance surrenale passagere n est jamais dangereuse *si l on a eu soin de ne pas suspendre brusquement la cortico*therapie mais d abaisser progressivement les doses Chez un de nos malades la suppression brusque de l A C T H à l occasion d un accident infectieux a ete suivie d une insuffisance surrenale aigue avec hypotension très marquee tachycardie et troubles de la conscience l administration de sérum glucosé et chloruré de desoxycorticostérone et de 200 mgr de cortisone a amené une sédation rapide

Nous avons traité sans accident des asthmes infectés mais nous avons soumis dans ces cas les malades à des doses plus elevees d antibiotiques Cette antibiotherapie preventive pose un problème delicat au cours des cures très prolongees doit elle etre continuee sans arret pendant des mois et ne perd elle pas dans ces conditions une partie de son efficacite? Nous avons vu en effet, apparaitre au quatrième mois d un traitement alterne par l A C T H et la cortisone une infection pulmonaire grave avec des foyers congestifs multiples et bilateraux bien que la tifomycine n ait jamais ete cessee La guérison a ete obtenue grace à l association d autres antibiotiques (penicilline et streptomycine)

Des troubles psychiques apparaissent parfois insomnies irritabilite Nous avons observe au cours d une cure d A C T H un syn

drome dépressif particulièrement grave qui a abouti au suicide

Nous n avons jamais noté même au cours des cures prolongées de symptomes sévères d hypercorticisme les sujets ont développé parfois une legère obésité avec aspect arrondi de la face de l acné mais n ont jamais présenté ni glycosurie ni hypertension artérielle ni osteoporose

Deux malades peu améliorés par une cure d A C T H sont morts dans un état de mal asthmatique l un vingt sept l autre trente quatre jours apres la cure hormonale Il est difficile de dire si l A C T H a joué un role nefaste dans ces deux cas Mais après les traitements par corticotherapie il nous semble prudent de soumettre les malades pendant plusieurs semaines a une surveillance medicale très rigoureuse et de recourir a un nouveau traitement par la cortisone en cas de rechute grave de l état de mal asthmatique

Les injections d A C T H peuvent entrainer une sensibilisation a ce corps nous l avons observé dans un cas au debut d une seconde cure, le malade a presente de l urticaire et une recrudescence violente de la dyspnee alors qu une première cure avait ete bien supportee

RÉSUME

Les auteurs ont traité 95 asthmatiques en etat de mal par A C T H cortisone ou hydrocortisone Ces trois hormones dont l activite est tres comparable ont permis d obtenir une sedation rapide des symptomes chez 80 malades Parmi les 15 echecs il y eut 4 morts l autopsie revela les lesions habituelles de l état de mal asthmatique

Les resultats à distance ont ete très variables 10 asthmatiques seulement beneficierent de la corticotherapie pendant plus de six mois

Chez 16 malades fut pratique un traitement hormonal prolonge (deux mois a trois ans) Il n y eut que 3 echecs et 1 résultat mediocre La dose seuil etait situee suivant les sujets entre 50 et 100 mgr d A C T H ou de cortisone par jour

N B Depuis que ce rapport a ete redige nous utilisons surtout la delta-cortisone

ACTH CORTISONE AND HYDROCORTISONE IN THE TREATMENT OF ASTHMA

A study based on ninety five cases

by

PASTEUR VALLERY RADOT CL LAROCHE AND GILLES LYON

We shall here report the results obtained in 95 patients affected with severe asthma and treated since 1950

All these patients were studied for over three months and 65 were studied for periods ranging from one to five years When treatment was started the patients were affected with status asthmaticus marked by dyspnoea which had continued for several days or weeks and which was aggravated by paroxysmal attacks Some patients were affected with cyanosis and tachycardia and in 5 cases even showed symptoms of right ventricular failure

These are the statistical data on our 95 patients

1) 58 patients were given a single treatment with hormones ACTH in 36 cases cortisone in 21 cases hydrocortisone in 1 case

2) 21 patients who had relapses were given several courses of treatment in succession

Of these patients 10 were given two courses of treatment in succession
- two treatments with ACTH in 4 cases
- one treatment with ACTH followed by one treatment with cortisone in 5 cases
- one treatment with ACTH followed by one treatment with hydrocortisone in 1 case

8 were given three courses of treatment in succession
- three treatments with ACTH in 4 cases
- two treatments with ACTH and one treatment with cortisone in 3 cases
- two treatments with ACTH and one treatment with hydrocortisone in 1 case

2 were given four treatments in succession ACTH being administered in one case cortisone in the other

One patient was given 22 successive treatments in four years i e approximately one treatment every two months ACTH and cortisone were given alternately

Accordingly, these 21 patients were given 48 treatments with ACTH 24 treatments with cortisone and 2 treatments with hydrocortisone

3) 16 patients were given prolonged treatments continued for over three months later we shall study the problems raised by this method

With the exception of the prolonged courses of treatment each treatment with ACTH or cortisone was continued for an average period of ten to fifteen days it was continued beyond this period when subsequent auscultation revealed the persistence of sibilant rales in the lungs or when the subject continued to have slight attacks or showed dyspnoea after exercise Therefore we continued to give hormones for twenty to thirty days in certain cases, the doses being progressively reduced

Dosage

ACTH was injected *intramuscularly* one injection being made every six hours when the initial doses were given When administering less than 100 mgm daily the injections were made at eight or twelve hour intervals

Fractionation of the doses is essential in view of the short action of the drug

In some cases we administered ACTH by *intravenous drip* very small doses of ACTH (10—20 mgm daily) dissolved in 500 ml of glucose solution, being slowly injected in a period of from six to eight hours The drawback to intravenous drip is that close supervision of the patient and especially of his blood pressure is essentail throughout the injection we never observed any marked rise in blood pressure in our patients however

Although intravenous drip afforded very rapid relief of the dyspnoea in some cases relief being obtained within four hours we do not believe this method to be more effective than intramuscular injections

In some cases we injected ACTH *intradermally* but the results were very inconstant Although extremely well tolerated by some patients the intradermal injections gave rise to painful local reactions in others and the hormone failed to have its usual effects owing to deficient absorption of the drug

We have recently used a solution of ACTH *retard* in 2 cases administration of this solution is advisable in prolonged treatment as less injections are required and the dose of hormone may be reduced When however rapid action is essential as in status asthmaticus ordinary solutions are to be preferred

Cortisone was administered intramuscularly in our initial cases subsequently the hormone was administered only by mouth the results obtained being equally satisfactory The latter method does not involve the risk of infection at the sites of injection The rapid action is even

increa ed by oral administration judging by the decrease of the number of eosinophils in the blood and the disappearance of the clinical symptoms

The daily quantity of cortisone given during the initial treatment was divided into four to six doses taken at equal intervals over 24 hours The doses were given at longer intervals when the dosage was reduced towards the end of treatment

Fractionation of the doses is even more essential when administering *hydrocortisone* than when giving cortisone as the action of hydro cortisone barely continues beyond six hours

Whatever hormone may be employed the initial doses should be large and then be progressively reduced

The initial doses of ACTH varied from 100 to 150 mgm daily given in four injections These doses were continued for three to eight days and then were gradually diminished

The doses of ACTH should not be reduced too rapidly an attempt should be made to obtain the complete disappearance not only of the dyspnoea and cough but also of the sibilant rales in the lung otherwise there is bound to be a rapid relapse This complete action of the hor mone is hardly ever seen to occur before the eighth day of treatment therefore a dose smaller than 75 mgm should not be given prior to the eighth or tenth day Treatments is concluded with the administration of small doses (50 and then 25 mgm) intended to avoid too sudden withdrawal of the hormone and to prevent secondary adrenal insuffi ciency rather than to exert a direct effect on the asthma Accordingly the average duration of treatment is from ten to fifteen days a total dose of 700—1 500 mgm of ACTH being administered this total dose varies markedly with the subjects

There is no relationship between the total dose of ACTH and the length of the remission Therefore it is useless to prolong treatment

When no improvement has been obtained after forty eight hours of treatment the dose may be increased e g to 200 mgm daily this will frequently have a favourable effect apparently there is a liminal dose for each patient below which ACTH is ineffective

When the status asthmaticus persists after three or four days despite administration of large doses of ACTH another hormone preferably hydrocortisone should be tried

Treatments with *cortisone* and *hydrocortisone* are governed by the same rules as those applying to treatment with ACTH

The initial dose should be fairly large 150—200 mgm of cortisone and 100—125 mgm of hydrocortisone being administered These dosages are

continued for three to eight days and subsequently reduced progressively to avoid complications resulting from sudden withdrawal of the hormone

As a rule the total dose of cortisone is somewhat larger than that of ACTH varying from 1 000 to 2 000 mgm administered within ten to fifteen days

The doses of hydrocortisone usually are 30 per cent smaller than those of hydrocortisone

Should courses of treatment wit ACTH be followed by administration of a few doses of cortisone or hydrocortisone and conversely should treatments with cortisone or hydrocortisone be followed by a number of injections of ACTH? This method has been suggested by certain authors with a view to preventing adrenal insufficiency In our opinion it is not a particularly useful method It is unlikely that administration of ACTH will result in an impairment of adrenal function or that treatment with cortisone will be followed by transient adrenal insufficiency

Results

The results obtained in treatment with ACTH cortisone or hydrocortisone vary markedly according as to whether the immediate results or the length of remission of the asthma after the completion of treatment are considered

These three hormones afforded more or less rapid relief of the functional symptoms in 80 patients We had 15 failures including a number of patients whose dyspnoea showed a slight improvement but who had persistent shortness of breath and continued to be subject to distressing paroxysms especially at night Of these 15 patients in whom treatment failed 4 died showing the classical symptoms of asphyxia and autopsy revealed the usual lesions of status asthmaticus characterized by marked obstruction of the bronchi

When treatment was effective it usually resulted in progressive relief of the dyspnoea and cyanosis and a decrease in severity of the paroxysmal attacks within the first twenty four hours the patients experienced considerable relief and were able to sleep again Slight attacks of dyspnoea persisted for 2—3 days and the slightest effort continued to cause a recrudescence of the shortness of breath Expectoration frequently decreased and occasionally even disappeared completely this drying up was attributable to the disappearance of the oedema of the bronchial mucosa resulting from the action of the hormones bronchoscopy revealed subsidence of the mucosa which again assumed a normal colour in some cases however bronchorrhoea continued to be profuse during a number of days but showed a mucous and fluid appearance Very often the eosinophils had disappeared from the expectoration as early as the second day of treatment

The sibilant rales in the lungs persisted for a number of days after relief of the dyspnoea

Accordingly treatment with these hormones frequently has a marked *immediate effect* on status asthmaticus The *late results* are much less excellent These are the results obtained

Ten patients with asthma benefited by treatment for a period of over six months fairly severe attacks recurred after six months in one case, after one year in 2 others and after two years in 2 other cases 5 other patients had not had any relapses of status asthmaticus after six months (1 case) two years (1 case) four years (2 cases) and five years (1 case) respectively

Remission did not continue beyond 3–6 months in 5 cases The symptoms disappeared for only 1–3 months in 14 others

All these subjects had been completely free from asthma at the end of treatment A slight dyspnoea after exercise persisted in some cases or attacks of dyspnoea readily controlled by the usual methods of treatment recurred but these patients had been able to resume a normal way of life

Relapses occurred within less than a month after treatment had been discontinued in 26 cases and as soon as it had been discontinued in 18 cases

We were unable to ascertain the length of the remission in 7 cases

Can the result of treatment be anticipated? Apparently the answer is no Whether the asthma is of allergic origin or due to superinfection of the bronchi, whether it is severe or not whether it is recent or long standing whether the patient is young or old the results cannot be predicted.

The recurrence of status asthmaticus led us to give *several courses of hormonal treatment in succession* (which have previously been described in detail)

These successive treatments enabled us to *compare the effectiveness* of ACTH cortisone and hydrocortisone in the same patients

We did not observe any noticeable difference between the effects of ACTH and those of cortisone the results obtained by administration of these two hormones usually are identical when they are used in the same patient The action of large doses (over 100 mgm daily) of cortisone administered orally is as rapid as that of ACTH and the degree of improvement as well as the length of the remission hardly vary with the drug employed Certain subjects however respond more readily to one hormone than to the other

It might be thought that the degree to which the adrenals respond to

corticotrophic stimulation in Thorn s test would afford a standard by which to judge the effectiveness of treatment with ACTH As we have stated in a previous paper [1] we have not been able to observe any parallelism between the decrease in eosinophilia and the effect of treat ment Patients who had negative tests showed a marked improvement on treatment with ACTH whereas failures coincided with positive tests Thorn s test is however known to have merely a relative value in subjects showing marked eosinophilia

Our experience of hydrocortisone has been too recent to enable any valid comparison with the two other hormones Nevertheless the first results obtained have been very satisfactory as no failures were observed in 10 courses of treatment with hydrocortisone And what is more we obtained good results in 5 patients who had failed to show any improvement on treatment with ACTH or cortisone Accordingly the effectiveness of hydrocortisone apparently is at least equal to and possibly surpasses that of the other two hormones

A certain number of authors believe that the effectiveness of the hor mones will decrease in patients given several courses of treatment with ACTH or cortisone Our findings have been different the results which we obtained in successive treatments were markedly identical

Despite the hazards attendant upon *prolonged treatment* with these hormones we subjected 16 patients to continued treatment These were patients with asthma whose dyspnoea had disappeared on hor monal therapy but recurred as soon as treatment was discontinued

Our first patients were given ACTH but to day we prefer using corti sone or hydrocortisone oral administration of which is more simple

The *duration of treatment* varied from two months to three years

Four patients were treated for over a year and excellent results were obtained Of these patients one has been treated alternately with cortisone and ACTH for the last three years the doses varying from 50 to 100 mgm daily This method afforded complete relief to another for a period of two years after which he was not seen again we learned that he had recently died from a vascular complication occurring independently of his asthma A third patient took 75 mgm of cortisone without a break during the past year The fourth patient who initially underwent continued treatment with cortisone (75 mgm daily) during

PASTEUR VALLERY RADOT LAROCHE CL MILLIEZ P DOMART A RENIER J-C L A C T H et la cortisone dans le traitement de l etat de mal asthmatique *Bull et Mém So méd des Hôp Paris* 68 195 319

[1] Some were studied by Dr B HALPERN

three years has now been taking 10 mgm of hydrocortisone six days a week for the last three months

Eight other patients were successfully treated with hydrocortisone for 2–3 months (3 cases) ACTH (1 case) cortisone followed by administration of hydrocortisone (1 case) ACTH and cortisone (2 cases) or all three hormones (1 case) Treatment was discontinued within two months in 2 of these cases without any relapse occurring Treatment was continued in the 6 other cases as discontinuation of treatment tended to result in immediate recurrence of the dyspnoea

We had only 3 failures and 1 moderate result in 16 patients A slight dyspnoea after exercise and some sibilant rales persisted in the greater part of the 12 others who led a normal life however they were no longer affected with permanent dyspnoea or paroxysmal attacks of asthma

The liminal dose below which distressing functional symptoms recurred varied from 50 to 100 mgm of ACTH or cortisone daily with the individual subject It also varied in a single subject however and tended to be increased by certain factors such as infection of the respiratory tract Within a few months the patients were able to conduct their own treatment using the minimum effective dose

Cortisone apparently became inactive in certain cases but when injections of ACTH were given for a number of days the subject again started to respond to treatment with cortisone

Turiaf[1] believes that it is advisable to administer cortisone and hydrocortisone for only five days a week but in some cases a two day interval will be sufficient to bring on a recurrence of the dyspnoea

Bickerman and Barach[2] have tried giving a large dose of cortisone (400 mgm) once a week but the results were extremely disappointing

The effective dose of hydrocortisone is smaller than that of cortisone According to Turiaf it is from 30–40 mgm daily

Recently we successfully used ACTH retard in the treatment of 2 patients one was given a daily injection of 40 mgm of this solution so that the dose of ACTH was reduced by two thirds in this case The result obtained in the other case with administration of 40 mgm of ACTH retard was identical to that of treatment with 75–100 mgm of ordinary ACTH 40 mgm of ACTH retard being more effective than 100 mgr of cortisone or 80 mgm of hydrocortisone

In our opinion it would be useful to make a number of injections of

[1] TURIAF J MASLAND P JEANJEAN Y Le traitement au long cours des asthmes à dyspnée continue par l hydrocortisone en comprimés *Revue des Praticiens* 4 1954 3037—3040

[2] BICKERMAN H BARACH A Comparative results of the cure of ACTH cortisone and hydrocortisone in the treatment of intractable bronchial asthma and pulmonary emphysema *J Allergy* 25 1954 312—324

ACTH every 4—6 weeks during prolonged treatments with cortisone or hydrocortisone with a view to stimulating the adrenals and preventing atrophy of these glands

Precautions to be taken to avoid complications and untoward reactions
ACTH cortisone and hydrocortisone are substances the use of which is not without danger They should only be employed wittingly in cases of severe asthma in which the usual methods of treatment have failed This restriction which we have formulated as early as 1952 continues to apply in our opinion

We systematically placed our patients with asthma on a salt free diet during treatment We gave them 1—2 gr of potassium chloride daily and we made them take an antibiotic (usually typhomycin or oxytetra cycline)

We never observed complications consisting in oedema or hyperten sion There were only slight gains in weight hardly exceeding 2—3 kg in addition the fact should be stressed that patients with severe asthma frequently show evidence of malnutrition and that a gain in weight coincides with a recovery of appetite therefore it cannot be attributed only to retention of water and sodium in every case

Within a few days administration of hydrocortisone frequently results in increased urinary secretion which may be transient or may persist throughout treatment in addition patients treated with this hormone often show a slight loss of weight Therefore retention of sodium is an unlikely event in these cases which is one of the advantages of treatment with hydrocortisone

Discontinuation of treatment is occasionally followed by moderate hypotension and asthenia this transient adrenal insufficiency is never dangerous provided that the hormone is not suddenly withdrawn and the dosage is gradually reduced Sudden withdrawal of ACTH in view of an infection occurring in one of our patients resulted in acute adrenal insufficiency associated with marked hypotension tachycardia and disturbances of consciousness administration of a glucose and chloride solution desoxycorticosterone and 200 mgm of cortisone afforded rapid relief

We have successfully treated cases of asthma complicated by infection but in these cases we administered larger doses of antibiotics to the patients This preventive treatment with antibiotics confronts us with a difficult problem during very prolonged courses of treatment should it be continued for months without a break and will not its effectiveness be reduced in these conditions? Thus a severe pulmonary infection marked by multiple and bilateral congestive lesions appeared in the fourth month of an alternating treatment with ACTH and cortisone

although administration of typhomycin had been continued throughout this period Combined treatment with other antibiotics (penicillin and streptomycin) resulted in the disappearance of the infection

Mental disturbances such as insomnia or irritability appear in some cases During a treatment with ACTH we observed a particularly severe depression which resulted in suicide

We have never observed severe symptoms of hyperfunction of the adrenal cortex not even during prolonged courses of treatment occasionally the subjects developed a slight obesity with a puffed face and acne but they never showed glycosuria hypertension or osteoporosis

Two patients who had shown little improvement on treatment with ACTH died in a condition of status asthmaticus one within twenty seven the other within thirty four days after treatment had been discontinued It is difficult to decide whether ACTH played a fatal part in these two cases In our opinion however treatment with these hormones should be followed by close medical supervision of the patients continued over several weeks and another treatment with cortisone is advisable if they should have a severe relapse of status asthmaticus

Injections of ACTH may result in sensitization to this substance this was seen to occur in one case the patient showing urticaria and a severe recrudescence of his dyspnoea when a second course of treatment was started whereas the first treatment had been well tolerated

SUMMARY

The authors treated 95 patients with status asthmaticus with ACTH cortisone or hydrocortisone These three hormones the effects of which bear a marked resemblance to one another afforded rapid relief of the symptoms in 80 patients Of the 15 patients in whom treatment failed 4 died autopsy revealed the usual lesions of status asthmaticus

The late results varied markedly only 10 patients treated with these hormones continued free from symptoms for a period of over six months

Sixteen patients were given a prolonged treatment with hormones (from two months to three years) There were only 3 failures and 1 poor result The liminal dose varied with the subjects ranging from 50 to 100 mgm of ACTH or cortisone daily

N B Since this report was written we specially use delta cortisone

LONG TERM TREATMENT OF ASTHMA WITH CORTISONE AND CORTICOTROPHIN

by

R S BRUCE PEARSON

Cortisone and ACTHAR gel are recognized to be of considerable value in the treatment of acute severe asthma. Their value as long term symptomatic remedies is less certain. In this paper the effect of treatment is recorded in twenty seven cases of intractable asthma with oral Cortisone (20) and intramuscular ACTHAR gel (8). One patient received treatment with both substances. Treatment was continued from three months to three years in 25 cases. In two side effects led to termination of treatment with Cortisone within a few weeks. Cases were selected for the chronicity of their symptoms. Thirteen had been admitted to hospital in status on one or more occasions and the remaining eight were included because of their failure to respond to other measures. Eight patients had been unable to earn their living or do more than light housework for at least a year and eight lost long periods of time from work each year. Three relatively mild cases were included.

Results were judged on vital capacity readings which were in most cases recorded every two weeks on a fast moving drum changes in attack rate and the quantity of spasmolytic drugs used and in the physical signs and capacity for work.

Dosage

Oral Cortisone was initially administered in doses varying from 300 to 100 mgm daily and maintained at 35 – 100 mgm daily. Larger doses were not administered owing to the risk of causing side effects. ACTHAR gel was given in doses from 40 mgm daily to 20 units weekly. Thirteen of the twenty seven patients were considered to have had excellent or good results (case 1 responded to both substances) one showed slight improvement and thirteen no response (See Table 1).

If these cases are divided into those with persistent expiratory wheezing in addition to attacks of dyspnoea and those with purely intermittent asthmatic symptoms it is evident that the results are very poor in the former group. These patients were never at any time found to be

[1] I wish to express my thanks to Dr D V Bates for carrying out lung function tests in two cases. Fifteen of the patients treated with Cortisone were included in the Medical Research Council's *Controlled Trial of effects of Cortisone acetate in patients suffering from chronic asthma* (in publication). The conclusions reached in this paper are those of the author only.

TABLE 1

Chronic or Recurrent Asthma (O Ps)

	No of cases	Results				Deaths
Treated with Cortisone		Excellent	Good	Slight	None	
Persistent expiratory wheezing	10	0	1	1	8	0
Intermittent asthma	10	2	4	0	4	0
Treated with ACTHAR gel						
Persistent expiratory wheezing	5	0	4	0	1	0
Intermittent asthma	3	1	2	0	1	0
Total	28	3[1]	11	1	13	0

[1] One patient who responded excellently to Cortisone and ACTH is included in both groups

free from evidence of expiratory obstruction whenever they were examined before or during treatment All had been under observation for at least one year and many for far longer

Treatment with Cortisone

Of the twenty cases treated with Cortisone ten had persistent wheezing and of these only two showed appreciable improvement of the ten with intermittent attacks six did well

Table 2 shows the results in ten of these cases who were each treated with Cortisone and Placebo tablets for alternate six month periods separated by three months of symptomatic treatment Eight cases were treated with the Placebo tablets for the first six month period and two with Cortisone Five of this group had chronic persistent asthma and five intermittent attacks None of those with persistent asthma improved Two (1 8) of those with intermittent attacks showed unequivocal improvement as regards attack rate and increase in vital capacity and on subjective and general clinical grounds One other (4) did well on Cortisone but even better on Placebo and was therefore regarded as a failure as far as the effect of Cortisone treatment was concerned another (10) claimed

TABLE 2

Case No	Sex	Age	Duration of asthma in years	Persistent Intermittent	Cortisone: Vital capacity	Cortisone: Attack rate for 2 week periods	Cortisone: Average daily dose in mgm	Placebo: Vital capacity	Placebo: Attack rate for 2 week periods	Symptomatic: Vital capacity	Symptomatic: Attack rate for 2 week periods	Weight increase on Cortisone
1	M	36	2	I	2570	3	81	2160	49	1810	36	+ 24 lbs
2	F	40	14	P	1500	42	70	1390	32	1420	21	+ 6 lbs
3	F	44	34	P	1840	30	94	1760	10	1850	14	+ 1½ lbs
4	F	31	12	I	2200	3 8	82	2340	2	1920	10 5	+ 11 lbs
5	F	40	14	P	1640	49[1]	100	1850	78	1600	10 2	+ 16 lbs
6	F[2]	51	17	P	1500	constant	70	1550	constant	1350	constant	+ 8 lbs
7	M[3]	41	9	P	1700	constant	100	2100	constant	2250	constant	No change
8	F	31	20	I	2370	7	100	2100	16	2020	47	+ 10 lbs
9	F[4]	41	1	I	—	—	75	1900	48	2600	23	—
10	M	36	8	I	3070	3	100	3700	1	2860	0 5	+ 14 lbs

[1] Injections of Adrenalin (self administered) were given 2—4 times daily during this period

[2] Attack rate not recorded but nebuliser used 7—10 times daily over whole period Emphysema present

[3] Constantly wheezy throughout taking 3—5 gr of Ephedrine and using inhaler 3—6 times daily Emphysema present

[4] Cortisone therapy terminated after 4 weeks because of depression

to be much improved on Cortisone but his attack rate did not reflect this and the vital capacity showed a considerably better average on the Placebo than on Cortisone Thus improvement in two cases was attributed to Cortisone in one to the effects of suggestion and in a fourth was mainly subjective and attributable to the feeling of well being caused by Cortisone The fifth case (9) with intermittent attacks improved suddenly during the fifth month on placebo tablets and remained almost free from asthma during the observation period of three months Cortisone was administered a month after relapse but was discontinued after three weeks because of severe depression No improvement took place in this time

Of the remaining ten cases treated with Cortisone but not with Placebo tablets good or excellent results were recorded in five one of whom had had severe persistent asthma of two years duration prior to treat ment One other case of persistent wheezing in a severe asthmatic of twenty five years duration improved temporarily but signs of heart failure due to cor pulmonale necessitated reducing the dose of Cortisone to 50 mgm daily which was below the effective level This patient was considered to have some emphysema Four of the cases who only had intermittent attacks responded satisfactorily

Side effects

Side effects were not serious One patient (9) became depressed another (14) developed oedema and complained of feeling ill due to a bursting sensation in her chest and face and a third (11) showed evidence of heart failure due to cor pulmonale A fourth (16) had a cough facture of a rib after 2½ years treatment it was considered that this might have been due to skeletal decalcification although this was not apparent radio logically Fourteen patients who continued on Cortisone for three months or more increased in weight from 6 to 24 lbs Three lost weight or increased by less than 2 lbs One patient (1) who had responded well during three months on Cortisone in doses between 50 and 75 mgm put on 15 lbs in weight Three patients with good response had considerable intensification of asthma shortly after termination of treatment and two of these (1 15) developed severe status within two weeks one of them (15) was admitted to another hospital where Cortisone was not administered and died in the attack Cases who showed no response to Cortisone were not upset even by sudden termination of treatment

Failure to respond on Cortisone

Details of the thirteen cases who responded only slightly or not at all are shown in Table 3 Four had emphysema (6 7 11 14) two of these and one other had their treatment terminated or modified because of side effects (9 11 14) Two patients (5 20) had nasal polyposis one with chronic antrum infection Cases with persistent expiratory wheez ing for periods of one year or more even if not accompanied by definite evidence of emphysema with one exception failed to respond to oral Cortisone therapy in the dosage employed by us Three relatively mild cases of intermittent asthma (4 10 13) also showed no appreciable response

Further possible reasons for failure to respond are considered in the discussion at the end of this paper

The following case histories are typical The first three responded successfully

TABLE 3

Failure to respond satisfactorily on long term Cortisone

Case No	Sex	Age	Lung damage	Persistent wheezing	Side effects	Weight increase	Duration of treatment	Average daily dose	Improvement but good or better response to Placebo
2	F	39	0	+	0	+ 6	6/12	70	0
3	F	44	0	+	0	+ 2	6/12	94	0
4	F	31	0	0	0	+11	6/12	82 5	+
5	F	40	0	+	0	+16	6/12	100	0
6	F	51	++	+	0	+ 8	6/12	70	0
7	M	41	++	+	0	— 1½	4/12	100	0
9	F	41	0	0	+		1/12		0
10	M	37	0	0	0	+14	6/12	95	+
11	F	49	++	+	0	— 1	6/12	73	—
12	M	37	0	0	0	+ 6	6/12	85	—
13	M	28	0	0	0	— 1½	6/12	95	—
14	F	32	++	+	+		2/52		—
20	F	49	0	+	0	+10	6/12	80	0

Clinical comments

2 Moderately severe asthma Emotional factor present

3 Moderately severe asthma Has never earned living because of asthma Emotional factor present

4 Emotional factor prominent Moderately severe asthma

5 Antrum infection intermittently for many years In hospital repeatedly with asthma Emotional factor present

6 Considerable emphysema Little evidence of infection

7 Considerable emphysema Little evidence of infection

9 Treatment terminated after one month owing to depression

10 Improvement mainly subjective Mild asthma only

11 Initial slight improvement Emphysema present Large emotional factor Has never earned her living because of asthma

12 Moderately severe asthma

13 A mild asthmatic Attack rate unaffected

14 Treatment terminated because of bursting sensation in chest Very severe asthmatic of long standing with evidence of lung damage

20 Nasal polypi Mild asthma with marked bronchitic tendency

remained persistently dyspnoeic on exertion Emphysema was present in this case The second patient was enabled to return to work and has remained relatively free from attacks for one year The remainder were all considered to have responded well judging by their former state but only one could be regarded as having remitted completely i e case 1 who had also responded well to Cortisone over a period of six months Two others were enabled to lead almost normal lives though one (27) was temporarily incapacitated as a result of bronchial infection after one year The remainder were all incapacitated to a greater or less extent

Five cases have now been receiving treatment for 1 year or more

Side effects

Side effects in this series were limited to increase in weight of 4 and 6 stones in two cases who presented the typical appearance of Cushing s syndrome although their asthma was incompletely controlled One of these (21) had definite evidence of emphysema The other patients have increased in weight by amounts varying from 12 – 16 lbs One patient (23) with a history of duodenal ulcer had a melaena

Failure to respond to A C T H A R gel

One patient (26) responded only poorly to ACTHAR gel a woman of 58 whose asthmatic attacks commenced at 45 diagnosed as severe asthma of undetermined origin with secondary infection Nocturnal attacks had been present for some years and recently had become worse with development of nasal polypi Repeated attacks of bronchitis also precipitated severe attacks She had been admitted to hospital in status at all times of the year on a number of occasions and on two occasions responded to ACTH when other treatment had failed A radical ethmoidectomy was carried out in November 1954 with little benefit Skin tests were negative After admission in March 55 she was given ACHTAR gel 10 units on alternate days As she became increasingly wheezy the dose was increased to 20 units daily and then to 40 units daily In spite of this her condition deteriorated she developed heavy infection with Str Pyogenes and Str Pneumoniae and was again admitted in status after three months treatment At her best this patient s vital capacity was well below the normal figure and persistent expiratory wheezing was present It is probable that her lungs were the seat of organic change

The following case histories are examples of the type of case treated

Case 23 *Male aged* 47 Severe asthma of indetermined origin which commenced insidiously on holiday three years previously Since then he had been almost continuously wheezy with severe exacerbations of his asthma No precipitating

causes were discovered his sputum contained some pus but pathogens were not isolated Although a highly nervous man no specific emotional factors were discovered He had spent five months out of fifteen in hospital prior to admission and had been bed ridden at home almost continuously consuming large quantities of symptomatic remedies He had responded temporarily to Cortisone in another hospital but he was said to have developed rigors which necessitated termination of treatment He at once responded to ACTHAR gel the vital capacity rising from 1 400 ml to 3 000 ml within a few days Attacks of dyspnoea still occurred and an expiratory wheeze was usually audible on examination His weight which was 8 stone when first seen increased to ten stones within a month In spite of restricted salt intake it has further increased by four stones on continued treatment with 20—40 units of ACTHAR gel daily during the subsequent eleven months He now presents the characteristic moon face and high colour of Cushing s syndrome Although he has not yet returned to work it is felt that there is no real reason why he should not do so he has not been confined to bed since his admission and has had no attacks which he has been unable to control His asthmatic state is however only partially controlled in spite of well marked hyper adrenalism

Case 27 *Male aged* 47 Intermittent asthma of bronchitic type A detective inspector who had suffered from duodenal ulcer in the past and had had asthma for 25 years He was a sensitive and nervous man whose attacks were precipitated by anxiety and bronchitis attacks occurred at all times of the year but were more frequent during the winter months These had been mild and infrequent until six years ago since when he had not lost much time from work During 1954 he was admitted to hospital and appeared to do well with an ACTH drip although the onset of improvement was delayed for 7 days As it was important for him to lose no further time from work and as his ulcer had given no cause for trouble for some years twice weekly injections of ACTHAR gel 40 units were given These were soon reduced to 40 units weekly and for the next five months he remained free from asthma He then had a melaena of moderate severity While in hospital his asthma recommenced and at his own request ACTHAR gel was continued with full ulcer therapy the asthma responded dramatically the vital capacity rising sharply He remained well for a further nine months on doses varying from 20—40 units weekly During this time he was able to carry out activities which he was formerly unable to undertake because of dyspnoea he has been able to control attacks of asthma by means of his atomiser and he has for long periods been free from all symptoms After one year he had an attack of bronchitis with which he was laid up for several weeks His weight increased by 10 lbs within a short time of commencing treatment and has persisted at this level which is not excessive for his height

Discussion

The result of long term treatment of 20 cases of intractable asthma with Cortisone are disappointing since only seven of the twenty were recorded as having good or excellent results Five of these cases only had previously received treatment with Cortisone or Corticotrophin as

in patients The eight cases treated with ACTHAR gel are not comparable *with the former group since all had been treated successfully* with Corticotrophin as in patients Seven of these continued to do well as out patients Those patients who had been subject to bronchial infections continued to develop fresh infections from time to time while under treatment and early recognition of these played an important part in maintaining them in reasonable health

Published results of treatment of ambulant asthmatics with oral Cortisone are shown in Table 4 Most authors have however carried out treatment for a few days or weeks only and have continued with long term treatment only in those patients who responded successfully in the first instance Savidge alone has employed placebo controls

TABLE 4

Ambulant Cortisone therapy	No of Cases	Good or Excellent	Fair	Slight or None
Irwin et al	23	23	0	0
Savidge & Brockbank	13	6	4	3 including 2 deaths
Friedlaender & Friedlaender	17	12	2	3
Arbesman & Richard	63	41	15	7
Blumenthal	30	22	8	0
Schwartz F	22	16	0	6 including 1 death
Lowell[1]	19	17		2
Present Series	20	7	0	13

[1] Lowell describes 17 cases as satisfactory

The possible reasons for failure will be briefly considered

Presence of organic disease of the lungs or of uncontrolled infection
Two patients (6 and 7) in the present series were considered to have had primary emphysema although this was not recognized at first owing to midleading histories These cases should clearly not have been included Two other patients (11 14) treated with Cortisone were thought to have emphysema secondary to their asthma one responded initially but the development of oedema and venous congestion necessitated a reduction in the dose of Cortisone below the effective level the other complained of a bursting sensation in the chest on 100 mgm daily and

treatment was terminated within two weeks Bronchiectasis affecting a small localised area of the middle zone of the right lung was present in one other (5) although there was no indication of persistent infection Arbesman Gay and others consider that emphysema or bronchiectasis are not incompatible with a reasonable response to endocrine sub stances One of our patients (21) with wellmarked emphysema did indeed respond satisfactorily to ACTHAR gel and when in status to intravenous Corticotrophin Three patients (5 20 26) had nasal polypi two of whom had repeated antrum infection all three failed to improve Bronchial infection was a complicating factor in many of these cases and recurrent infections were not prevented by endocrine treatment Infection was in all cases controlled at the commencement of therapy

Inadequate dosage
The dosage employed was similar to that used by most workers If more than 100 mgm of Cortisone or 40 units of ACTHAR gel are given daily over long periods of time serious side effects are likely to develop

Inadequate absorption of Oral Cortisone
Friedlaender has pointed out that this may occur He describes a patient who responded to I M Cortisone but who failed to respond to oral Cortisone This may have accounted for failure in two of our patients (3 13) whose weight remained approximately stationary during six months of treatment with an average daily dose of 94 mgm and 100 mgm of Cortisone

Side effects
Treatment was terminated after three weeks in one patient (9) because of depression and after two weeks in another (14) who also had lung damage In one case with emphysema (11) the dose of Cortisone was restricted because of oedema and evidence of cor pulmonale

Emotional factors
Emotional factors were thought to have contributed to the maintenance of asthma in ten patients prior to treatment with Cortisone or Corticotrophin Five (2 3 4 5 11) failed to respond to Cortisone but five (8 16 17 21 23) responded satisfactorily to Cortisone or Corticotro phin There is therefore no evidence that emotional factors account for failure to respond in the present series

It has not been possible to explain failure as the result of any single cause and in a number of cases no satisfactory reason has been dis covered Although moderate lung damage is not incompatible with some improvement the presence of fibrosis or emphysema clearly inter feres with a satisfactory response The recognition of such lung damage

is however not always easy even with the assistance of lung function tests as Beale et al have pointed out

Not only must we accept that a proportion of chronic asthmatics will fail to respond satisfactorily over a long period of time to Cortisone or Corticotrophin in reasonable dosage but as Lowell et al have stressed few of the cases who respond well can be recorded as having fully recovered normal lung function Attacks of asthma still occur from time to time the tendency to acquire bronchial infections is unaffected and in many the vital capacity remains reduced or the expiratory rate is greatly prolonged Only one (1) of our 27 cases a man of 36 with severe intermittent attacks of 2 years duration could be regarded as having been restored to normal throughout the period of treatment with A C T H Two patients (one on Cortisone and one on A C T H) have been enabled to return to work but six are still not working one of these is considered fit to work but has not yet decided to do so Three others have lost less time from work than in the year before treatment

Conclusion

The value of Corticotrophin or Cortisone as a long term method of controlling symptoms in chronic asthma is limited In a mixed group of cases with longstanding symptoms many failures may be expected these may be partly explained by the presence of organic changes in lungs or bronchi side effects or with oral Cortisone because of inadequate absorption The effective dose of Cortisone or A C T H varies considerably from case to case and does not appear to be related to the severity of the symptoms of asthma Objective methods should always be employed as far as possible in assessing results The use of placebo treatment will demonstrate that some patients apparently responding to the effects of Corticoids have in fact undergone spontaneous remission or improved as the result of suggestion Side effects in the doses used have not proved troublesome except for the tendency to put on excessive weight depression heart failure and melaena occurred in one case each

References

ARBESMAN C E RICHARD N B *Journ All 25* 1954 306
BEALE H D FOWLER W S COMROE J H *Journ All 23* 1952 1
BLUMENTHAL, J S *Lancet 71* 1951 473
FRIEDLAENDER S FRIEDLAENDER A G *Journ All 22* 1951 291
GAY L N MURGATROYD G W *Journ Mich gan State Med Soc 53* 1954 33
IRWIN J W HENNEMANN P H WANG D M K BURRAGE W S *Journ All 25* 1954 201
LOWELL F C SCHILLER I W LEARD S E FRANKLIN W *Journ All 24* 1953 112
SAVIDGE R S BROCKBANK, W *Lancet 2* 1954 889
SCHWARTZ E *Journ Amer Med Ass 147* 1951 1734

INTRODUCTORY LESSON ON HORMONAL TREATMENT OF BRONCHIAL ASTHMA

by

H J TEN CATE

Prolonged treatment of asthmatics with adrenocorticotropic hormon

Although treatment of short duration with ACTH may be life saving in severe asthmatic state a prolonged remission of the asthmatic symptoms is seldom observed

Especially patients with severe continuous asthma mostly belonging to the elder age group where in all probability endogenous (endocrine?) causes are more important than exogenous (allergic) causes are apt to relapse within a few weeks

An attempt at prolonging the treatment by one weekly intravenous slow drip infusion of ACTH in 5 per cent glucose solution succeeded only at a single patient

Prolonged treatment at home by 6 daily intramuscular injections is not practicable

The long acting ACTH preparations seemed more efficient for prolonged treatment at home

At the Chest department of the Groningen university clinic of internal medicine two long acting preparations are used The first preparation owed his prolonged effect to the binding at carboxymethylcellulose referred to as ACTH C The other preparation owed his prolonged activity to the adding of zinc referred to as ACTH Zn

Before using these preparations for treatment their effect on the blood eosinophils of asthmatics and normal persons were recorded and compared to the effect of ordinary ACTH of the same batch Basic conditions like at the Thorn test were required

According the effect on the blood eosinophils the long acting preparations have their strongest effect 8–12 hours after the injection Their effect on the adrenals seems stronger than the effect of ordinary ACTH The effect of the long acting preparations on the asthmatic symptoms also was strongest 8–12 hours after the injection and disappeared within 24 hours

The observation that daily injections of the long acting preparations act stronger against the asthmatic symptoms as the injections of the double amount every other day agrees with this

As prolonged treatment with ACTH may cause serious side effects we only submitted patients to it when other measures and treatment

were unable to prevent disability or to prevent perilous attacks

The treatment always started on the hospitalized patient mostly after a short treatment with ordinary ACTH After discharge the treatment was continued at home under supervision of the out patient department for chest diseases The patients came once weekly afterwards once in 2 to 3 weeks for reexamination and control

Besides physical examination laboratory procedures were involved like examination of sputum (eosinophils and Gram) urine (albumine reducing substances and urobiline) plasma electrolytes and haematocrite eosinophils respiratory function circulation time weight

To prevent or to correct shifts of the plasma electrolytes it was necessary to prescribe a low sodium diet and additional potassium chloride (2–6 g daily)

Besides the effects on the asthmatic symptoms the stimulation of the adrenals resulted in the gaining of weight by fat deposition moon face acne pigmentations Edema was not frequent no more was a rise of the arterial tension ACTH preparations also are able to provoke allergic manifestations We observed urticaria Quinckes edema and dyspnoea at a few patients especially with the intravenous drip method of ordinary ACTH

The next two tables serve to give an impression of our results with the two long acting preparations

Three patients received (hydro) cortison

The 22 patients are divided into 3 groups namely patients with exogenous asthma (exo allergy) demonstrable especially for many inhalant allergens patients with endogenous asthma no allergens demonstrable as causes of asthmatic symptoms and a group with mixed causes they demonstrated allergy to foods (2) and aspirin (1) but also demonstrated symptoms after elimination of allergens Of the group endogenous asthma some patients experienced allergic symptoms but no asthma after sulfa and chinidine and ACTH (treated with cortison) grass pollens (only rhinitis)

Some patients of the groups endogenous and mixed asthma demonstrated complications like cor pulmonale bronchiectases emphysema often in combinations Some of these patients repeatedly suffered broncho bacterial infections

A good result means no further hospitalizations were necessary Only few patients demonstrated freedom of symptoms during periods of some months A bad result means during treatment further hospitalizations were necessary Most patients felt better during treatment than before

To sum up our experiences on treatment with long acting ACTH preparations at asthmatic patients

TABLE 1

Groups	Number of pat	Ages	Duration of treatment	Results		Died
				good	bad	
Exogenous	4	15—25 y	2—10 months	1	3	0
Mixed	3	44—65 y	8—38 months	2	1	1
Endogenous	15	39—70 y	6—33 months	8	7	4

TABLE 2

Duration of treatment	Number of patients	Results		Died
		good	bad	
2— 6 months	6	1	5	3
6—12 months	7	4	3	2
12—24 months	5	4	1	0
24—36 months	3	2	1	0
36—48 months	1	0	1	0

1) Prolonged treatment necessitates low sodium diet and additional potassium chloride (2 – 6 g daily)

2) During treatment broncho bacterial infections are no more frequent than before treatment at the same patients

3) Daily injections of long acting preparations cause better clinical results than the double amount injected every other day

4) The daily amount of the long acting preparations has to be adapted to the changing needs of the patients Mostly a daily dose of 5 – 15 U suffices

5) Increasing eosinophilia rising to high levels (60 per cent–4000/mm^3) is often a precursor of aggravation of the asthmatic state

6) Other therapeutic measure readily can be carried out during treatment Hyposensitization symptomatic treatment (antihistaminics) treatment with antibiotics and cardiotonics (digitoxine digoxine)

7) Changing the 2 long acting ACTH preparations may be succesful

when the clinical effect of the used preparation has decreased Changing into cortison also may be succesful when both long acting preparations afford no longer effect

Sometimes it was necessary to hospitalize the patient again and treat him with ordinary ACTH Afterwards the long acting preparations again were used with sufficient result

8) Most frequent side symptoms of treatment were gaining weight moon face acne pigmentations Less frequent were edema and rising of the arterial tension

9) The results of treatment are not overwhelming However it must be taken into account that only selected asthmatics were submitted to prolonged treatment who underwent several other treatments without success and whose prospects were bad

The best results are scored in the groups with endogenous and mixed asthma The lowest results in the group with exogenous asthma Adrenocorticotrophic hormon insufficiently protects against allergens although experimentally some protection seems to be afforded

DISCUSSION

ANTI HISTIOCYTIC AND ANTI ALLERGIC ACTION OF CORTISONE*

by

LINO BUSINCO

In 1954 we have published the results of a study regarding the action of cortisone on the morphology of the organs One of the most striking observations has been for us as for the other authors who have studied the phenomenon the structural modification of the lymphoid organs and particularly of the spleen In this regard the lymphocytolytic action of cortisone is often mentioned The detailed histological study permits to recognize that the negative action of cortisone on the lymphoid organs and particularly on the spleen is not exercised upon the lymphocytes but upon the histiocytic component represented above all by the cells of the germinative centers In fact a first microscopical examination permits to see a reduction of the cellular elements of these organs which have been treated with cortisone And in this reduction are comprised of course also the lymphocytes But the principal negative action is exercised as we have now said essentially upon the histiocytes of the germinative centers We notice here above all an extensive edema and various signs of cellular trouble (cytoplasmatic dilatation nuclear pycnosis and fragmentation rupture of the cellular body and so on) These regressive phenomenons of the histiocytes are accompanied parallely by an evident reduction of the peripherical lymphocytic mantle that is directly tied to the alterations of the histiocytic matrix

Being established that these histiocytes of the germinative centers have a part of the greatest importance in the production of the antibodies it is clear that cortisone develops the antiallergic action in a particular manner acting against the histiocytes of these centers The morphologic and functional alterations brought about by cortisone upon the histiocytes deranges at its basis the mechanism of the reaction of the antibody against the antigen And during this stage of cortisonian histiocytic suffering we have the best therapeutic anti allergic results of the hormone

When the administration of cortisone is stopped the histologic study reveals in the germinative centers a quick reconstitution of the histiocytic patrimony this reconstitution can be observed clearly at the microscope in a surprising wealth of caryokineses By means of this strong proliferation movement the germinative centers return to their normal morphological constitution and the tissues get rid of the last cellular leavings Once regained the normality of the histiocytic patrimony the antibody function of these centers takes up full action again and then we have the relapses of the allergic syndromes

This parallelism between the integrity of the histiocytes and the allergic reactions proves once more the importance of these cells in the immunitary and particularly in the allergic functions

* From the Institute for Medical Semeiology at the University of Rome

W J QUARLES VAN UFFORD *

Time and again it is amazing to observe how treatment with ACTH administered by intravenous drip (possibly combined with aminophylline) will result in the dis appearance—if only temporary—of a status asthmaticus or bronchial asthma A long term treatment is much more difficult and the result obtained less striking Cases of chronic bronchial asthma—in which every form of specific treatment has failed—are bound to recur sooner or later in an equally severe form when treatment with ACTH is discontinued Apparently administration by intravenous drip has the advantage—as has frequently been observed—that good results are even obtained in cases in which courses of treatment with cortisone or intramus cular injections of ACTH have failed This is of special importance in the event of a third or fourth course of treatment as the patient recalling the striking results obtained previously will be acutely disappointed when improvement fails to occur We have frequently been struck by the fact that the patient when ad ministration by intravenous drip (a form of treatment which often is extremely unpleasant to him or her) proves difficult is not relieved when the physician at a loss what to do proceeds to administer a larger dose by intramuscular drip and finally a dose of a preparation of ACTH having a prolonged action requesting him instead to continue with the intravenous drip as this method is more effective in his opinion

We used the following methods in the long term treatment employed in fifty patients over a 4-year period

a) administration of 25 (or more) mgm of ACTH by intravenous drip once or twice weekly if need be combined with administration of aminophylline An antihis taminic was given prior to the intravenous drip and 0 3 ml of adrenaline was injected intramuscularly at the beginning of treatment to prevent possible allergic reactions

b) treatment with varying doses of cortisone and ACTH administered by intra venous drip once every 6 weeks In addition this opportunity was used to examine the blood sugar urine ECG etc

c) treatment with cortisone alternating with a course of injections of a prepa ration of ACTH having a prolonged action likewise combined with ACTH adminis tered by intravenous drip every 6 weeks the examinations also being made on this day

In view of the fact that this treatment was used only in almost hopeless cases the results may be stated to have been highly satisfactory The patients includ ing those previously disabled were almost always rendered fit for work again Meanwhile constant efforts were made to develop a specific therapy

There were 5 patients with complications

a) one patient with an insulin controlled diabetes who was given 3 courses of treatment with ACTH prior to the long term ACTH therapy which involved a temporary increase of these dose of insulin to be administered although the longterm treatment did not result in aggravation of the diabetes

b) three patients who became pregnant during treatment in whom several previous pregnancies had failed to produce any improvement of the asthmatic

From the Allergic Department of the Diaconessenhuis Utrecht (Dir Dr M A van Melle)

symptoms—the very reverse occurred—and in whom treatment was continued during and after pregnancy without giving rise to any untoward reactions

c) a patient with silicosis affected with bronchial asthma and subject to asthma like attacks due to the silicosis whose symptoms disappeared completely during the period of treatment Being impatient he discontinued treatment after one year whereupon all the symptoms recurred in full force

Of the patients treated by these methods 5 died as the years went by

1) One died from acute heart failure three months after treatment had been discontinued (this was a 25 year-old girl who had previously been treated with pneumectomy which operation was followed by the recurrence of asthmatic symptoms which were more severe than those observed at any time in the past)

2) Suicide committed by an older patient who had been harbouring suicidal thoughts for several years prior to treatment however

3) *Acute heart failure in a 13 year old boy whose father had continued treatment* himself in view of the excellent results and had refused any examination

4) A severe and uncontrollable attack of dyspnoea in a 37 year-old woman in whom treatment had been discontinued at the request of the family practitioner and also for financial reasons

5) An acute severe attack of dyspnoea terminating fatally within a few minutes in a 56-year old man in whom treatment had been considerably reduced owing to bronchopneumonia The patient had shown symptoms of fatigue coughing increased expectoration and a markedly increased ESR for a long time previously Treatment with antibiotics had resulted in the disappearance of these symptoms and so far there had been no signs of dyspnoea so that small doses of ACTH were constantly administered until a very acute brief severe attack of (cardiac?) dyspnoea caused the death of the patient

Those patients however who are restored to normal life from a state of constant illness and disablement make combined treatment with ACTH and cortisone a valuable addition

ACTH HYDROCORTISONE AND PREDNISONE IN THE TREATMENT OF BRONCHIAL ASTHMA *

by

UMBERTO SERAFINI and UBALDO DI NARDO

We report our findings on the treatment of bronchial asthma with ACTH hydrocortisone and prednisone But before we do this we would like to expose briefly some preliminary experiments on the therapeutic activity of these preparations

We first studied the adrenal response as expressed in the behaviour of the peripheral eosinophils to intravenous ACTH in three series of experiments

In the first of these series we established the smallest biologically active dose when ACTH was given rapidly in 30 seconds intravenously Generally a drop of more than 50 per cent is obtained with 4 mg

From Istituto di Patologia Speciale Medica University of Florence and Istituto di Clinica Medica Generale University of Rome

The second series was concerned with the duration of adrenocortical stimulation studied in two ways Firstly by varying the duration of the intravenous infusion from 2 to 8 hours with a fixed dose of 20 mgm ACTH We found that the longer the duration of the infusion the longer is the duration of the eosinophilic drop below 50 per cent

On the other hand when the duration of the infusion is kept constant at 8 hours and the dose is varied from 5 to 20 mgm the duration of the eosinophilic drop increases with the dose

In the third series of experiments we studied the intensity of the adrenocortical stimulation and found that when the time was varied and the dose kept constant at 20 mg the intensity of the response depends directly on the duration of the infusion But when the duration of the infusion is maintained at 8 hours and the dose varied the intensity of the response is relatively independent of the dose

In order to establish the adrenocortical response of asthmatic patients to ACTH we subjected 15 such patients to Renold s 8 hour test It was found that asthmatic patients react in the same way as normal persons Moreover in asthmatic patients the eosinophilic drop evoked by 12 daily infusions of ACTH or by prolonged treatment with cortisone differs in no way from that seen in normal persons

Regarding the relationship between ACTH and ascorbic acid we found that when ACTH is given by intravenous infusion there is an initial urinary loss of vitamin C which may exceed the amount administered In a second series we found that adrenocortical stimulation as expressed in the eosinophilic drop also occurs in vitamin C deficiency However the response lasts longer and is more intense when the body is saturated with ascorbic acid

This means that when ACTH is given therapeutically ascorbic acid should be given as well for the double purpose of replenishing the Vitamin C lost in the urine and in order to prolong and intensify the adrenocortical response

ACTH given either intramuscularly or by intermittent or continuous intravenous infusion hydrocortisone and prednisone have produced better therapeutic results than can be obtained by any other method We obtained favourable results in 85—90 per cent of our cases However it must always be remembered that we are dealing with remissions of symptoms and not with cures

We are convinced that in asthma it is indispensable to make detailed etiological studies in every case sothat when indicated desensibilization can be undertaken with lasting results

Symptomatic remissions obtained by the use of hormones may be total or partial depending on the degree of reversibility of the underlying morbid condition It should however be remembered that before we can judge a result to be negative we must have assured ourselves that the preparation used is active and that the dosage has been adequate We had to do this several times when using compound E of F When ACTH is being given intramuscularly we must also be sure that we are not dealing with a case of socalled ACTH resistance

Regarding the results obtained with ACTH given by the intermittent or continuous intravenous route it can be said that though the percentage of favourable results is the same the improvement is not as marked as with the intramuscular route On the other hand the intravenous infusion has certain undeniable advantages over intramuscular administration Far smaller doses can be used the onset

of relief is much more rapid and the dosage can be more finely adjusted Obviously it is the only method in those rare cases in which ACTH given intramuscularly is inactive

With hydrocortisone the dosage is particularly low and thus eliminates significant side effects such as may occur with ACTH and cortisone This makes it possible to continue treatment even for several weeks Hydrocortisone is therefore particularly indicated in cases of ACTH allergy

The recently introduced prednisone[1] must undoubtedly be regarded as one of the most significant advances in cortisone therapy We have only used it in a limited number of cases and cannot therefore express a final opinion on its efficacy but in the cases we have studied we found it markedly more active than cortisone and comparable with hydrocortisone yet significant side effects were less than with any other similar hormone We can report on 10 patients suffering from severe asthma of long duration who were given 30 mgm daily by mouth during the first days after which the dose was gradually reduced until a maintenance dose of 15—20 mgm was reached Treatment lasted from 7—15 days The results were excellent in 7 good in 2 medium in 1 In this case the daily dose was 60 mgm for 7 days without giving rise to side effects The same patient obtained an equally poor result from a subsequent treatment with hydrocortisone The period of remission is about the same as that achieved with hydrocortisone The secondary effects were an increase in weight of some patients and insignificant changes in arterial pressure and in diuresis In no case was glycosuria seen

A comparative study undertaken by us of the eosinophilic drop induced by the oral administration of cortisone and prednisone showed that the latter produced an identical effect with only one third the amount Studying 10 normal persons we found that in man one obtains the same eosinophilic drop as is evoked by 50 mgm cortisone with 15 mgm prednisone These data at our knowledge are the first published in the world medical literature concerning bronchial asthma

Owing to the fact that the partial or total remission of symptoms depends as we said on the greater or lesser reversibility of the underlying morbid condition we use ACTH and the cortical steroids as a test by which to judge the reversibility of the asthmatic emphysema In fact in cases of continuous bronchial asthma that can look like real emphysema hormonal therapy in adequate dosage establishes whether the symptoms are reversable or definitely irreversable Apart from its diagnostic value this is of course of great prognostic and therapeutic importance

Among the very large number of cases studied in recent years we have encountered only 6 cases of ACTH allergy that manifested itself as asthma or anaphylactic shock

It is therefore necessary to stress the practical importance of regularly testing the sensibility to ACTH whenever treatment is repeated

The observation of one case in which 50—100 mgm ACTH given intramuscularly produced neither a clinical remission nor an eosinophilic drop both of which were obtained by giving as small a dose as 2 5 to 5 mgm intravenously suggests

[1] Prednisone is the designation given to delta 1—4 pregnadine 17 alpha 21 diol 3 11 20 trione by the Council on Pharmacy and Chemistry of the A M A which was previously known as metacortandracin

that intramuscular ACTH may be incapable of producing a metabolic response not because the adrenocortical response is insufficient but because certain conditions of the tissues prevent the ACTH from passing into the circulation This might also explain the decrease in the efficiency of ACTH which is not uncommonly seen in subsequent treatments Possibly the hormone may be inactivated in the tissues when there is no clinical response or in those cases in which the intramuscular Thorn s test is negative which would then not mean that there is an adrenocortical deficiency

The authors previous publications on the subject of this paper

SERAFINI U ARGENTI M DI NARDO U NAPOLITANO L Risultati della terapia con l ormone adrenocorticotropo ipofisario in varie condizioni morbose *Atti del 52° Congr della Soc Ital di Medicina Interna* Roma 1951

DI NARDO U Sull eosinopenia prodotta da ACTH e cortisone *Progresso Medico* 8 502 1952

SERAFINI U FRANCESCHINI G MAFFEI R DI NARDO U Osservazioni cliniche sulla somministrazione endovenosa di ormone adrenocorticotropo ipofisario *Clin Terap* 3 12 1952

SERAFINI U ARGENTI M DI NARDO U NAPOLITANO L Risultati terapeutici conseguiti con ormone adrenocorticotropo ipofisario *Progresso Medico* 8 589 1952

ARGENTI M DI NARDO U Ricerche sulla tecnica di determinazione degli eosinofili nel sangue periferico *Policlinico se med* 60 1 1953

SERAFINI U DI NARDO U Studi su alcuni effetti dell ACTH somministrato per via endovenosa nell uomo Nota 1 La dose minima biologicamente attiva somministrata per via endovenosa *Boll Soc Ital Biol Sper* 29 1742 1953

SERAFINI U DI NARDO U idem Nota 2 Comportamento dell eosinofilia ematica dopo infusioni endovenose di durata varia con dosi costanti di ACTH *Boll Soc Ital Biol Sper* 29 1745 1953

SERAFINI U DI NARDO U idem Nota 3 Comportamento dell eosinofilia ematica durante e dopo infusioni endovenose di durata costante con dosi variabili di ACTH *Boll Soc Ital Biol Sper* 29 1748 1953

DI NARDO U L ACTH per infusione endovenosa nel rattamento dell asma bronchiale *Folia Allergol* 1 91 1954

DI NARDO U Idrocortisone Ricerche sperimentali ed applicazioni terapeutiche in allergia *Folia Allergol* 1 414 1954

SERAFINI U DI NARDO U Studi su alcuni effetti dell ACTH somministrato, per via endovenosa nell uomo Nota 4 Modificazioni della entità dell eosinofilopenia conseguente alle variazioni della dose e della durata della somministrazione di ACTH per infusione endovenosa *Boll Soc Ital Biol Sper* 40 965 1954

DI NARDO U ERRIGO E Rapporti tra chimismo gastrico ed assorbimento del cortisone somministrato per via orale nell uomo *Boll Soc Ital Biol Sper* 30 969 1954

DI NARDO U MALIZIA E Effetti dell ACTH sulla ascorbinuria e sull attività adrenocorticale in soggetti carenti e saturi di vitamina C *Riv Clin Med* Ottobre 1954

DI NARDO U ERRIGO E Assorbimento del cortisone per via duodenale nell uomo Atti del II Congr Naz di Allergia Napoli 1954 in *Folia Allergol* 2 Fasc 2 1955

DI NARDO U ERRIGO E Variazioni del chimismo gastrico in pazienti asmatici durante trattamento con cortisone ed idrocortisone Atti del II Congr Naz di Allergia Napoli 1954 in *Folia Allergol* 2 Fasc 2 1955

SERAFINI U DI NARDO U La risposta surrenale allo stimolo corticotropo negli asmatici — Atti del II Congr Naz di Allergia Napoli 1954 in *Folia Allergol* 2 Fasc 2 1955

SERAFINI U BORGHI A PIERI A Inefficacia della somministrazione intramuscolare dell ACTH — Atti del II Congr Naz di Allergia Napoli 1954 in *Folia Allergol* 2 Fasc 2 1955

SERAFINI U PIERI A. DI NARDO U Impiego del prednisone nell asma bronchiale *Minerva Medica* Giugno 1955

ANTIBIOTICS IN ASTHMA

by

JACQUES DUCHAINE

The discovery of penicillin and its commercial production at low cost was heralded around 1946 as one of the most important steps in the treatment of those two troublesome forms of asthma the so-called intrinsic asthma and the atopic asthma with bacterial infection

About the same time a new technique of introduction of drugs into the bronchial and pulmonary fields by inhalation of aerosols was being widely experimented and the conclusions were that aerosolisation of penicillin was the most economical effective and logical manner in which to bring the drug directly in close contact with the infected mucosa From 1946 to 1949 much work on that line was done in most European countries and in the U S A

If the immediate aim was the search of a more effective medium to neutralize the consequences of infection in asthma a secondary but all the most very important idea was to put to an acid test our prevailing theories concerning the influence whether toxic or allergic of bacteria on the different forms of asthma

To day after nearly ten years of experimentation it seems possible to re appraise the whole question and to verify if our hopes have been even partially fulfilled

Is treatment by penicillin (injections aerosols or per os) a worthwhile procedure in infective asthma? Have the results obtained with anti biotics given us a better insight in the probable mechanism of infection in asthma and the related diseases?

When the published results of antibiotic therapy are studied one striking fact appears immediately a fact that previously does not seem to have held the attention it deserved The authors can be divided in to two groups those who use what may best be named supportive measures (mostly aerosols of aminophyllin or adrenergic bronchial dilators sometimes broncho aspiration or inhalation of helium oxygen etc) before or during the inhalations of penicillin and those who do not use these measures and prescribe only injections or as in most cases aerosols of the antibiotic Unfortunately in some cases it is not always clear which precise technique was used but nevertheless in five papers respectively by Prigal et al [8] [9] Farrerons Co [4] Findeisen [5] San giorgi [10] and Duchaine [2] who specify their results statistically it appears that supportive measures (aerosols of broncho dilators) were used in

conjunction with the antibiotics All the patients thus treated can be classified as cases of secundary infected allergic asthma, chronic infectious bronchitis or intrinsic asthma Out of a total of 424 patients, results were favourable in 343 (81 per cent) and unfavourable in 81 (19 per cent) Conclusions can best be summarized in the words of Segal [11] Best results can be obtained if the bronchial passageways are patent, we employ aerosols of Vaponephrin or Aleudrin 1 200 preceding the neo synephrin penicillin aerosols

The opinions of those who do not use supportive measures is at definite variance with that expressed here above In only two papers have we been able to find statistical evidence of the poor results obtained by penicillinotherapy when no broncho dilator drugs are used simultaneously Of 123 patients treated by Engelster [3] and Prigal et al [8] only 40 (32 per cent) had favourable results and 83 (68 per cent) were not relieved

Segal in another paper [12] confirms this Such therapy is generally disappointing Olsen [7] Results have been temporary and disappointing in our cases of asthma Gay [5] Penicillin and sulfonamides were equally useless to the majority of sufferers from an infectious type of asthma

At this point it seemed logical to conclude that any or most of the benefit that could be derived from penicillin aerosols, should be attributed much more to the supportive measures than to the bacteriostatic virtues of the drug

Therefore we tried a modest experiment During three months all of those patients to whom previously we would have prescribed a series of penicillin + adrenergic aerosols were put to a course of exclusively bronchial dilator drugs (adrenalin + theophyllin), without penicillin or any other kind of antibiotics At the end of the treatment and six months later results were grossly assaied in terms of physical signs presence or absence of sputum of dyspnea on exertion tightness of the chest feeling of well being

Although it is especially difficult to found an opinion on statistics which rely so much on the patients subjective judgement, we may say that all considered results with adrenalin + theophyllin were practically equivalent with those obtained with adrenalin + penicillin What seemed one of the characteristic influences of penicillin the thinning of the sputum with its conversion of purulence was as easely gained with theophyllin As with penicillin results were temporary and relapses followed more or less rapidly

To what reasons must we ascribe the failure of a drug which has been revealed so powerful in other diseases? We can only speculate on this question and state the issues without answering them

1) The bacteria responsible for the symptoms of infective asthma are not those like streptococcus viridans which we habitually find in the bronchial secretions and most of which are penicillin sensitive Maybe we are in fact dealing with little known organisms or perhaps viruses

2) So called infective asthma is not due to bacteria or it may be that the foci of infection are so deeply imbedded in the folds of the mucosa that the antibiotics cannot reach them

3) In the so called bacterial allergy bacteria probably have much less importance than the lesions they have induced We know that these lesions are irreversible contrary to those due to atopy which are reversible with rapid restitutio ad integrum once the allergens have been removed or neutralized The accent here is more on the consequences of the cause than on the cause itself

4) In atopy it is most probable that infection (especially infection of the nose and auxiliary sinuses) acts as a trigger mechanism For this reason antibiotic treatment is always started too late and is power less to stop the consequences brought by the spreading of the inflam mation to part or the whole of the respiratory tract

Is it to say that penicillin is useless in asthma? Far from it and it is our opinion that it has a definite value against infection in a closed cavity If pulmonary abcess is rare in asthmatics infection of the auxiliary sinuses is a very common complication of respiratory atopy and penicillin is very effective against it especially in children

Although the newer antibiotics (tetracycline chloramphenicol erythromycine etc) should be used in well defined circumstances (whooping-cough pneumonia pulmonary abcess etc) I do not believe that they have been tried on any large scale in ordinary bacterial or in infected asthma The price of these drugs is still prohibitive and they may not be devoid of dangerous reactions if given for a long period

The new French antibiotic *Framycetin* obtained from Streptomyces Descaris [13] has in vitro a broader spectrum of action than penicillin or streptomycin It is at present times at least very active against most strains of staphylococci but it is too toxic to be injected and must be used locally or by aerosols From a very limited experience I can say that it does not appear to give any better results than penicillin and it seems to be more irritating to the respiratory mucosa It is still in the experimental stage and the only results yet published have been those of A Biron [1] with 36 good 6 fair and 2 unfavourable results out of 44 cases but according to the author 3 or 4 drops of Aleudrin 1 100 solution were added to the antibiotic

Complications with penicillin are rare but should not be dismissed too lightly Five or six years ago penicillin aerosols often provoked

lesions of an irritative nature in the mouth or the pharynx (black tongue), but these were due to an imperfect purification of the drug and they are now very rare On the other hand I have been witness to a fatal case in a man 45 years of age sufferer of intrinsic asthma for the last twenty years who died within five minutes after the injection of 1 million units of procain penicillin As this patient was known to be aspirin sensitive it is probable that the generalized shock was due to a latent sensitivity to the procain (or para) radical and not to the penicillin itself

At this point it is important once again to sound a word of warning There is no doubt that fungic antibiotics and specially penicillin are used without discrimination Although they now appear to be harmless enough we do not really know what changes they may bring about in the organism of patients who have been submitted year in year out to this therapy In my practice where most pollensensitive patients are routinely tested with 36 different fungi extracts I find an increasing number of positive reactions to extracts of penicilium notatum reactions without clinical significance at least at the present time but what may happen in the future is unknown

Another point which we should bear in mind is that neither penicillin nor streptomycine are potent enough to sterilize even for a short time the respiratory tract Antibiotic therapy is only indicated if we can be reasonably sure to kill right off the most noxious bacteria The danger of favouring the appearance of penicillin resistant strains is a real one although little experimental work has been done on this line in asthma

What is the present status of the problem of antibiotics in asthma? I hope that many of our colleagues from different countries will be able to give their opinion on this question I can only tell you how I feel about it Clinical work on asthmatics is a specially time consuming procedure and we really should not appraise our results unless the patient has been under observation for at least one year while he undergoes the stresses of daily life in both its favourable and unfavourable circumstances

Last year impressed by the fact that congestion and inflammation are the main injurious symptoms in asthma I used mainly hydrocortisone or ACTH in conjunction with the better tolerated and most active sulfonamides (gantrisin elkosine or supronal) At that time these antibiotics were prescribed to avoid any spread of the infection which could have been brought about by the hydrocortisone The ease of this procedure which does not need any injections is among others one of its strong points Results in cases of atopy with infection were strikingly good when used in combination with ordinary desensitizing measures in

infective or intrinsic asthma results were much less favourable although somewhat better than with penicillin But relapses were frequent and the sulfonamide hydrocortisone therapy tended to wear off its effects as courses had to be repeated

This year my tendency is more or less to do away entirely with antibiotics (penicillin or sulfonamides) and use hydrocortisone alone It is too early yet to conclude from a limited experience but again I must emphasize the fact that if atopic patients do very well on such a therapy results in the long standing cases of chronic infectious asthma are far from good Rational therapy of these lies still in a treatment consistant with the needs of the individual patient and where vaccination hydrocortisone and antibiotics can all play their part

Conclusions

1) Antibiotics should be used in well defined and limited cases where there are signs of localized infection (pneumonia broncho pneumonia bronchiectasis pulmonary abcess infection of the sinuses etc) and not in the forms of protracted bronchial congestion

2) An effective antibiotic is still to be found for those cases where infection of the upper respiratory tract acts as a trigger mechanism

3) As far as we know hydrocortisone alone or used in conjunction with antibiotics is the most effective therapy of infection in asthma

R ferences

1 Biron A Etude du sulfate de Framycét ne en aérosoltherap e dans 198 cas de broncho pneumopath es *P esse Méd 63* n .7 p 551 1955
2 Duchaine J La bronchite chronique *Le Poumon 4e année* 1948 p 271
3 Engelster D L Aerosols of penicillin *Journ Am Med Ass 131* 61 1946
4 Farrerons-có F J Penicilina en ae osol para el tratamiento de bronqu tis asmat ca bronqu ectasia y enfisema *Acta Méd Hispanica* n 36 1947
5 Findeisen D G R Erfahrungen mit der Aerosol Inhalat onsbehandlung des infektions alle gischen Asthmas *A ta All 6* 4 p 312 1953
6 Gay L N *The D agnosis and Treatment of b onchial Asthma* Williams and Wilkins Company 1946 p 322
7 Olsen A M D scuss on in *Jou n Am M d Ass 134* 9 p 769 1947
8 Prigal S J Morganbesser L J McIntyre F P P nicillin ae osol in the pre ... and treatment of resp ratory infections in allergic patients *Jou n All 18* 3 5 1947
9 Prigal S J Furman M L The use of Bacitracin a new antib otic in aeroso ... *Ann All 7* p 66 1949
10 Sangiorgi P Aerosoltherapia antib otica dell asma bronchiale batterico *Quad ...* n ? 1949
11 Segal M S *The manag ment of the patient with seve e b onch al asthma* Charles ... Springfield USA 1950 p 123
12 Segal M S Levinson L Miller D Penicillin inhalation therapy ... fections *Journ Am M d A s 134* n 9 p 76 1947
13 Soas C Trocme Y La sof amycine en thérapeutique pneumologique ... n 17 p 365 1954

ANTIBIOTIC TREATMENT IN ASTHMATIC PATIENTS WITH BACTERIAL BRONCHITIS

by

J MULDER

Bacterial muco-purulent bronchitis is often observed both in the acute and in the chronic form in asthmatic patients The bacterial flora is the same as in the non asthmatic group The table shows the distribution of this bacterial flora in 296 cases of acute and chronic muco purulent bronchitis including asthmatics and non asthmatic patients

TABLE I

Incidence of the bacterial flora in 296 cases of acute and chronic muco-purulent bronchitis (combinations are left out)

H influenzae	76 per cent
Pneumococcus	25 per cent
Neisseria	8 per cent
Staphylococcus aureus	5 per cent
Klebsiella	4 per cent
Escherichia coli	3 per cent
Streptococcus viridans	2 per cent

In about 80 per cent of the cases of chronic muco purulent bronchitis (for the most part associated with bronchiectasis) we found symptoms of asthmatic bronchitis (e g sputum eosinophilia)

If in an asthmatic patient the bacterial flora is eliminated by antibiotics the patient continues to expectorate sputum in which the neutrophylic leucocytes for the most part are replaced by eosinophils The result of antibiotic treatment on the asthmatic condition in general is not very great though marked improvement may follow especially in acute cases Some asthmatic patients suffering from chronic muco-purulent bronchitis may even get worse and show heavy asthmatic attacks In some way the chronic bacterial inflammation interferes with the tendency to bronchospasm The explanation of this fact is not clear Most patients however feel much better after the elimination of the bacterial inflammation because the quantity of sputum diminishes considerably and the chronic intoxication ceases Unfortunately the bacterial inflammation relapses very often after some weeks or months especially in cases associated with chronic anatomical bronchial changes (stenosis and bronchiectasis)

Inflammation caused by H influenzae can be eliminated by 4 million units of penicillin per day (1 million units every 6 hours)

The combination of penicillin and streptomycin (0 5 g every 12 hours) is preferable and it is probable that with this combination less penicillin is necessary Streptomycin alone shows a failure in about 50 per cent of cases owing to bacterial resistance Chloramphenicol and the anti biotics of the tetracyclin group are effective in a dosage of 2 g per day We treat most patients for a period of 10 days

In acute pneumococcal infections a treatment with 300 000 to 600 000 units of procaine penicillin is sufficient Chronic pneumococcal infections are very rare in asthmatic patients Acute pneumococcal bronchitis however is rather common

DISCUSSION

P J VAN DER WERFF

I was much impressed by Prof Mulder s lucid demonstration of several problems in the field of bronchobacterial inflammations relating to bronchial asthma and by his very thorough and accurate investigations and his accordingly highly reliable findings

For a long time we in the Amsterdam Clinic of Allergic Diseases have made grateful use of all advice on his own special method of investigation of the sputum [1] and on therapeutic measures [2]

With permission I would ask Prof Mulder three questions

1) What is your opinion on the possible causes of the phenomenon mentioned by you and also observed by myself viz a severe bronchospasmodic aggravation which occasionally occurs when antibiotics are administered prior to anti allergic *treatment in chronic bronchial asthma with secondary bacterial inflammation?*

2) Do you think that there is a probability of a primary origin of bronchobacterial asthma and if so do you have objections to the initial administration of antibiotics in these cases?

3) Do you believe that there is usually an underlying latent (i e non manifest) allergy?

J MULDER

1) I do not know for certain which mechanism accounts for the fact mentioned by Dr van der Werff Perhaps a cause might be that bronchospasm is counter acted by the inflammatory tissue reaction in the submucosa and smooth muscles of the bronchi Every inflamed smooth muscle tends to lose its tone causing dilation of the hollow organ to which it belongs

Another hypothesis brought forward by Dr Orie in Groningen is that the inflammation causes a stress reaction associated with more ACTH production

2) & 3) I have the impression but no proof that some asthmatics start their disease after sinusal or bronchial infection caused by viruses or bacteria but only when there is an underlying latent allergic tissue condition

H COLLDAHL

I would draw attention to the fact that in many cases of asthmatic bronchitis the bronchial secretions taken by bronchoscopy are sterile Further I think that the pulmonary tissue in asthmatics must have a particularly high resistance against bacterial infections How can this be explained by the bacterial findings of Mulder I should like to ask how this discrepancy can be explained

[1] References a o MULDER J Thesis Groningen *1937 Ned T v Geneesk 92 3521 1948*

[2] PLAS M C VAN DER Thesis Leyden 1951

J MULDER

The pure asthmatic sputum is sterile which can also be shown by carefully washing the flakes in buffered saline and studying the strains The discrepancy between the frequency of bronchial infections and pulmonary infections in asthmatic patients can easily be explained because H influenzae causes only bronchial infections and not, or only very rarely pneumonia and the serological pneumo coccal types in bronchitis are generally of the higher types of Cooper which do not readily invade the lungs

ACTINOMYCIN C IN THE TREATMENT OF ASTHMA*

by

LINO BUSINCO

The eminently lymphotrope action of actinomycin on one side and the relations existing between the lymphatic system and immunity on the other side have led us to the research of a possible influence of actinomycin c (Sanamycin) both on anaphylaxis and on the allergic syndromes The research has revealed that actinomycin c does not succeed in avoiding the mortal crisis which befalls the guinea pig as a consequence of the re injection of albumen However it has revealed that in the animals treated with actinomycin c the crisis has had a longer duration

On the contrary actinomycin c has exercised a favourable influence on human allergy The treatment by means of daily intravenous injections of small doses of Sanamycin (usually from 40 to 150 micrograms) lasting for three weeks at the most has allowed us to attain a good percentage of probing results In fact on 7 cases of bronchial asthma we have had 2 excellent results 3 good ones 1 poor and 1 null on 7 cases of urticaria the results have been excellent 3 times good 2 times once poor and once null In a case of colitis the result has been only poor We have had favourable results even in cases of inveterate and rebellious bronchial asthma in chronic urticaria they have been at times surprising

The doses we have administered have not brought about any trouble with the exception of some transitory gastro intestinal pains However in the guinea pig the autopsy data do often reveal a phlogosis of the gall bladder therefrom the necessity to apply an appropriated diet as well as to establish the advisable therapeutic measures in the patients suffering from hepatic troubles

Regarding the details of our observations the following must be emphasized

In the guinea pig the fur often presents a certain brittleness and the single hairs fall easily off The gall bladder is often considerably dilated and at the post mortem examination it is found to be inflamed Contrarily to what has been stated by other Authors the number of the red and white blood cells has not undergone any important changements At this point it is necessary to emphasize that the decrease of the number of the eosinophils which has been observed in the allergic patients treated with Sanamycin is in perfect agreement with the favourable results obtained by this treatment

Attention must be drawn quite particularly to the results of the electrophoretic examination of the plasma proteins The researches which have been performed

From The Institute of Medical Semeiology University of Rome

on the guinea pig as well as on allergic patients demonstrate that the treatment with actinomycin c causes a substantial diminution of the globulins and above all of the gamma globulins it is known that these last ones are considered as the carriers of the antibodies The meaning of this decrease could be understood in the following interpretation by acting on the lymphoid tissue which is in charge of the formation of the antibodies actinomycin c deprives it of this important function

It follows that the action on the lymphoid tissue is accompanied by a lowering of the rate of the gamma globulins and as a consequence of the antibodies *This decrease of antibodies can justify from a humoral point of view the improve* ment which is usually to be observed in the allergic patients under the effect of Sanamycin By diminishing the rate of antibodies the treatment deprives the antigens of an important part of the material upon which they react therefrom the improvement of the clinical condition

ANTIBIOTICA THERAPY

by

HELGE COLLDAHL

When one has to decide in a case of asthma if antibiotica therapy ought to be given the first question is this is there any infection present or not? According to an investigation which I had the opportunity of presenting the day before yesterday asthmatic patients with no apparent increase of BSR were not found to have *bronchial infection more frequently than persons with healthy lungs*

Asthmatic patients with elevated BSR had bronchial infection more often than persons with healthy lungs An elevated BSR is according to my opinion the best sign of a complicating infection

A slight temperature elevation can depend upon increased muscular work from breathing difficulties and must not be interpreted as a sign of infection

In the above mentioned investigation the bronchial secretion for culture was collected by catheterisation through a tracheal tube under general anesthesia with Evipan and Scoline I think that this method is the most exact one to employ when *investigating as to whether bronchial infection is present or not With this* method a differential count of the bronchial secretion will give further evidence of the presence of a bronchial infection In this case neutrophilic leucocytes are often in excess even if a marked increase of eosinophils is present When no infection existed eosinophils were found preponderant in the secretion In all infected cases there was mucopurulent or purulent sputum but in most cases without bronchial infection sputum was of the same appearance A mucopurulent sputum therefore in our opinion is not necessarily a sign of bronchial infection It can certainly depend on the allergic process itself Even in cases with a negative skin test there is in the bronchial secretion often an enhancement of eosinophilic leucocytes indicating in all probability that allergic factors are of significance although the antigen is unknown As the eosinophils specially are in excess when no bronchial infection exists it is unlikely that the antigen in these cases is of bacterial origin A possible explanation might perhaps be that the antigen is formed from destroyed bronchial tissue

We found bactenal infection in our asthma material in 25 per cent of the cases examined

When suitable antibiotics are administered to asthmatic patients with bronchial infection, the asthmatic troubles often become aggravated. In such cases a combination with antibiotics and ACTH is indicated

References

BERGMAN S COLLDAHL H NILSSON E *Acta Allergol VIII* 163 1955

FURADANTIN

A NEW ANTIBACTERIAL AGENT IN INFECTIONS OF THE RESPIRATORY ORGANS

A preliminary report

by

H CHR PAULSEN

1) The bacterial flora in infections of the respiratory organs present great variations and the treatment results are to a high degree dependent on the resistance against antibacterial therepy of the bacteria concerned in each case

2) In most cases the usual antibiotics will give satisfactory results but there wil always remain some cases in which these agents prove insufficient. Therefore there will always be a need of new agents for the treatment of infections of the respiratory tract

3) In 1944 Dodd and Stillman found that certain furan compounds could be given new antibacterial properties by addition of a nitro-group to the molecule Thus we got a new preparation—Furadantin (nitrofurantoin)—which was found to have a broad antibacterial spectrum with very rare occurence of acquired resistance and with low toxicity

4) Furadantin is a yellow crystalline substance soluble in water It is resorbed quickly and almost completely from the intestine Even in the case of large doses the blood concentration has been found to be low (Palmløv and Tunevall) and the preparation has therefore been of no importance in infections of the respiratory organs

5) The nitrofuran derivatives attack the bacteria by destroying certain enzymatic processes necessary to the vital functions of the bacteria The mechanism is evidently of a different character from that of sulfonamides and antibiotics which involves that acquired resistance against the latter agents does not make itself felt in the use of the nitrofuran preparations As a matter of fact it has been found difficult often impossible experimentally to create resistance against nitrofuran derivatives in bacteria that can be influenced originally

6) The antibacterial spectrum of Furadantin is very broad including grampositive as well as gram negative microbes Bacteriostatic and frequently also bacteriolytic effect is thus had in most strains of Escheria coli, Staphylococcus pyogenes albus and aureus Streptococcus pyogenes Klebsiella and Proteus vulgaris

7) In vitro has been found that strains of staphylococcus aureus streptococcus mitie streptococcus pyogenes and Escheria coli showed no tendency to permit development of resistent bacterial strains (shown by Mintzer Kadison Schlaes and Felsenfeld at Hektoen Institute for Medical Research Cook Country Hospital Chicago) and Grayson Carroll gave in February 1955 information of staphy lococcus sensitive to Furadantin in 44 strains none resistent

8) Originally I started this work as a new treatment of Proteus vulgaris which is a frequently occuring microbe in chronic nose affections and rhinitis and it is found not infrequently in our asthma and emphysema patients with chronic bronchitis ectasis fibrous pulmonary changes with major mechanic obstructions and protracted retensions It is also found in patients that have been subjected to intense penicillin treatment It is found almost exclusively in adults—especially elderly people—and I have never found it in children Dick Henriksen found the Proteus vulgaris group in 5 per cent of a material consisting of 180 cases in his work intitled Studies on the bacterial flora of the respiratory tract in acute and chronic bronchitis bronchial asthma and lunggangren (1937) and 5 7 per cent in the group chronic bronchitis bronchial asthma This group further contained

Pneumococcus	12 5 %
Staphylococcus albus	16 3 %
Staphylococcus aureus	19 2 %
Haemophilus influenzae	7 7 %
Streptococcus	63 5 %
Escheria coli	43 0 %
Klebsiella	10 0 %

Haemophilus influenzae is very sensitive to Furadantin and on account of this *used as testbacterium*

9) Streptomycin treatment has rendered good service in cases of Proteus vulgaris but it has not always given satisfactory results It therefore seemed natural to try a nitrofuran preparation considering the good results that had been achieved with this agent in cases of Proteus in the urinary tract but the obstacle was the low blood concentration that was possible to obtain and that did not produce any effect in infections of the upper respiratory tract and the lungs The only possible way of obtaining a satisfactory effect was then to use Furadantin in local treatment with aerosol various solution strengths (produced in co-operation with the A B Pharmacia Uppsala Sweden) have been tested and the experiments are going on

Furadantin has been combined with Tween 20 (polyoxietylensorbitanmonolaurat) which has no antibacterial effect but its physical activity are a liquifying effect and lowering of the surfacetension both of value in the treatment with Furadantin —and antibiotics too—which reach the bacterium easier and with better effect and perhaps have some influence on the tendency of resistance

The side effects were insignificant 1 out of the 38 patients subjected to this treatment showed symptoms of nausea but it was not necessary to interrupt the treatment Other side effects mentioned in the literature are emesis and one isolated case of skinhypersensitiveness which disappeared after removal of the

preparation but the doses u ed in aerosoltreatment are very small in comparison with that of infection in the urinary treat Until further experience is g ined it is advisable to check the blood during the treatment In my cases no blood change has been proved

10) *Case I* was a male of 55 years with fibrous top changes and planigraphic actasis in the right side, where strong growth of Proteus vulgaris and staphylo coccus aureus were found both sensitive to streptomycin, chloromycetin—and staphylococcus to penicillin too The patient was treated with streptomycin 15 grams and chloromycetin 15 grams and penicillin without effect Renewed test during first 32 days revealed continued strong growth of Proteus vulgaris and staphylococcus aureus with positive plasma coagulase reaction Aerosol treatment with Furadantin solution was begun and after 7 aerosol treatments there were no longer any proteus vulgaris nor staphylococcus aureus to be found—and the patient became afebrile Test after 5 months showed that there was still no growth of Proteus vulgaris nor staphylococcus aureus

11) *Case II* was a male of 44 with asthmatic bronchitis Culture of the expectorate revealed growth of Proteus vulgaris—sensitive to chloromycetin terramycin and sulfatiazol He was treated with terramycin but the treatment had to be disconti nued because of allergic reaction He was then treated with Streptomycin peni cillin and thyrosolvin inhalation (6) with positive effect He had a relapse a month later and was given aerosol treatment with Furadantin solution which removed the symptoms 3½ months after the end of the treatment there was still no Proteus

12) *Case III* was a male of 65 with asthmatic bronchitis and rhino sinusitis (vasomotorica) Radiograms of the accessory sinuses showed induration in the sinus frontalis ethmoidalis and antri Heavy growth of Proteus vulgaris from both sides of the nose with relative resistance against Furadantin Aerosol treat ment was resorted to all the same and the patient reported improvement of the rhinitis after two treatments —after the third treatment negative physicals above the lungs and improved respiration After 7 treatments there was still profuse growth of Proteus vulgaris Considering the radiograms finding in the accessory sinuses it was not likely that the Proteus vulgaris would disappear —as access from the more deeply situated sinuses maintained the infection

13) I started this work with treatment of infections of Proteus but it was very soon proved that Furadantin had a good effect on other bacterial pulmonary infections—in some of these cases antibiotica had had no effect—and after treatment with Furadantin solution, used in 38 cases the results achieved so far seem to indicate that in this drug we have found a new antibacterial agent with good effect and low or no toxicity Particularly I want to mention again the fact that resistant strains of staphylococcus streptococcus and Escheria coli are never demonstrated—an important fact in consideration of the strong growing tendency of increasing infections due to antibiotic resistance Here staphylococcus aureus is the most typical illustration

14) Infection with penicillinresistant staphylococcus aureus increase now as a consequence of the antibiotic treatment From a series of hospitals all over the world reports have been given of strains of staphylococcus which exist inside the hospitals are resistant to penicillin to a greater extent than staphylococcus outside the hospitals

Publications 1943—44 revealed about 12 per cent of resistant strains In Copenhagen Erna Lund demonstrated an increase from 16 per cent in 1947—48 to 59 per cent in 1949—51 Laurell and Wadmark found in 1953 staphylococcus isolated from patients at a pediatric department 68 per cent and from the hospital staff 83 per cent staphylococcus resistant to penicillin In some departments of the Epidemic Hospital in Stockholm practically all the staff had staphylococcus aureus resistant to penicillin When we know that staphylococcus have resistance to streptomycin aureomycin and terramycin up to 45 per cent we may say that it is a dangerous development Strains of resistant staphylococcus aureus are now one of our great problems

It appears to me that Furadantin offers much promise for the treatment of bacterial infection in the respiratory tract through its effectivity and lack of resistance to staphylococcus aureus It seemes that Furadantin is to prefer to the large doses of penicillin and streptomycin mentioned today

The preliminary results arrived at induce to continue the work and the results will be reported later

FOCAL INFECTION AND ALLERGY

by

H A E VAN DISHOECK

Local inflammatory processes affect more or less markedly particularly in the acute phase the entire organism When the local inflammation is chronic—either with or without exacerbation—it is called an inflamma tory focus These focal infections may follow a course without or prac- tically without local and general symptoms It is generally believed that such inert foci are nevertheless capable of setting up serious morbid symptoms in remote organs Diseases mentioned in this connection are inter alia the collagen affections such as acute and chronic articular rheumatism neuritis iritis nephritis endocarditis myalgia chorea and some forms of asthma The foci may be present in inter alia the tonsils the secundary nasal cavities the teeth the gallbladder the pelvis and the intestine With regard to the manner in which the infection focus may cause such diseases as arthritis and asthma various assumptions suggest themselves

Bacteriaemia

In the first place the germ might pass from the focus into the blood stream and thereby provoke a temporary bacteriaemia and toxaemia This is the idea which Osler formulated when calling the tonsils the porte d entree for rheumatic infection Also Billings stated that clinical observation had demonstrated the existence of such temporary bacteri aemia beyond all doubt Direct proof of this type of bacteriaemia how ever is difficult But there is one observation that argues in favour of its existence i e the fact that following tonsillectomy bacteria were found in the blood It is further known that in cases of articular rheumatism an attack often occurs after tonsillectomy In such cases therefore we have both bacteriaemia and attacks This clearly suggests the conclusion that an invasion of bacteria was the actual cause also in former cases of angina followed by an attack

In all diseases in which bacteria are found in internal organs and in which invasion either in continuity or via the lymphatic system is im possible as in endocarditis transport via the bloodstream must be assumed Invariably the question will then be at what point the blood stream was infected The rational reply to this question will have to be that the infection most probably occurs at the point where there exists an inflammatory focus and where therefore the bloodstream and the

bacterial flora are in close contact This is the case f i in the tonsillar crypts in an infected regional lymph gland or in a dental abscess In particular one should here think of an infected thrombus as the cause of the germ s passing into the bloodstream In accordance with this conception Bolck and Arndt found in 57 out of 70 tonsils of rheumatic patients deeply penetrating into the peritonsillar tissues severe chronic inflammation often accompanied by phlebitis

This conception of a metastatic infection or mild sepsis therefore implies that the bacteria coming from the focus nestle either temporarily or permanently in the remote organ and may therefore be cultivated from the diseased organ as in endocarditis Presently the conception that endocarditis lenta should be a weakened sepsis caused by streptococci tamed by their host cannot be maintained The investigation of Griffith and Lancefield learned that the pathogenety of the streptococcus is linked to its chemical and immune biological properties Thus the streptococci of the polysaccharid containing A group are the cause of angina scarlatina and erysipelas whereas endocarditis lenta is caused by the milder viridans group

In asthma notwithstanding the vaccin therapy which is based on the assumption that bacteria or their products enter the bloodstream such a mild sepsis is never proved

Toxaemia

In the second place it is thought possible that although no living germs may pass into the bloodstream—or that if they do they will soon be killed—but that their toxins and decay products definitely do enter the circulation This re absorption of bacterial products chiefly via the lymphatic vessels is probably a continuous process whose intensity depends upon the activity of the focus

A wellknown example of the direct toxic action of a bacterial focus on a remote organ is diphtherial myocarditis as Billings already stated to support his argument

In asthma as well as in rheuma such a re absorption of bacterial proteins is very probable but the tissue damage caused by these products is not so marked as in diphtheria

Allergization

Allergization of the organism by bacterial products is a widely known phenomenon It must be assumed that against foreign protein re absorbed parenterally immune antibodies will be formed in the body These processes have been studied with both clinical and experimental accuracy with respect to e g tuberculosis and rheumatic fever In addition to immunization however there is also sensitization These

two phenomena although both allergic in nature must nevertheless be viewed as separate entities It is precisely in diseases caused by focal infections that sensitization and the reactions caused by it are prominent and of the utmost importance for our understanding of bronchitis and asthma

Animal experiments to imitate allergic tissue changes

An example of a disease which is even more than asthma thought to be due to an infection focus is articular rheumatism Countless experiments have been made in the course of the years in order to provoke this affection in animals with the aid of the bacterium that causes it in man These experiments have not been entirely successful although it has proved possible to produce formations closely resembling Aschoff s nodules This effect was obtained by the repeated infection of the animal with streptococci A single infection might perhaps kill the animal but never produced the effect in question Thus a prelimary sensitizing infection is obligatory for the allergization of the animal In addition these experiments are only successful in a limited percentage of laboratory animals In others—for reasons as yet unknown—the disease fails to develop a fact which is analogous to the human form of the affection The observation of Murphy and Swift that in the positive cases there is hypertrophy of the adrenal cortex points to the correlation of these diseases with that organ Pagel has pointed to the two fundamental pathologic anatomic symptoms in allergy viz

1) in the presence of much reagin and allergen oedema bleeding and necrosis i e the phenomenon of Arthus

2) in the case of less violent and more prolonged action granulomatosis The Aschoff s nodules belong to this latter group

The Shwartzmann phenomenon

In this respect the Shwartzmann phenomenon is also important Shwartzmann showed that by first injecting the skin of a rabbit with a bacterium free filtrate of a culture followed by a second intravenous injection of the same filtrate he produced local necrosis This proves that bacterial products are capable of sensitizing a tissue and that the supply of the allergen through the bloodstream can produce a reaction Later on another extremely important observation by Shwartzmann and Sanarelli was added to this viz that the second intravenous injection need not even be of the same culture To provoke such a hetero allergic reaction requires extremely sensitive animals and a large quantity of filtrate This reaction is far less frequently successful than the specific one

Recently Thomas and Stetson have provoked the Shwartzmann phenomenon by producing focal infections with haemolytic streptococci

in animals followed by the injection of a number of bacterial toxins They then observed the occurrence in a number of laboratory animals of a generalized Shwartzmann phenomenon consisting in haemorrhagic necrosis near the foci bilateral necrosis of the adrenal cortex and cardiac lesions strongly resembling rheumatic affections This type of experiments has given the focal infection theory a sound experimental basis

Organ localization

A third series of experiments is also of great importance for the proper understanding of focal infection in connection with its localization in particular organs The basal phenomenon was described by Auer who found that when a sensitized animal had been brought into a state of protracted shock by sub-lethal injections of allergen an intensive phenomenon of Arthus could be produced by rubbing xylol into the animal s ear Kümmel gave the first sensitizing injection into the eye and found upon re injection through the bloodstream that the reaction was localized in the eye Even an injury alone is enough to produce a localization of the reaction in the injured organ Thus nephritis may be provoked in an animal sensitized to a serum foreign to its species by a second injection in which a special nephrotoxin has been added to the serum Kallos investigations have shown that in an analogous manner localization in the heart can be obtained by means of caffeine while according to Vaubel cooling can have a similar effect on a joint

Clinical consequences

The over enthusiasm as well as the waning enthusiasm of physicians to remove all tissues that might possibly harbour pathogenic germs must be attributed to lack of proper knowledge of the problem It is undeniable that there are distinctly successful cases but it is necessary not to pitch one s expectations too high We are in fact justified in concluding on the ground of animal experiments and clinical observation that an infection focus sensitizes the body and that the re absorption of bacterial products may act as an intravenous re injection Whether such a re injection will result in an attack cannot be predicted either in animal or in human cases *Any reaction will preferably occur in an organ which* had already passed through an infection by the germ or which had *been injured in some other way There is no doubt that these processes* are far more complex than we can realize on the ground of our present immunological knowledge

Explanation of disappointments

The disappointing continuance of attacks after the removal of the focus may be linked up with the unspecific Shwartzmann phenomenon Even if an infection focus that was probably the initial cause has been done

away with it is nevertheless possible for other bacterial products occasionally to arrive in the bloodstream from other places and to provoke fresh attacks *It is also possible that the primary focus has already done* so much damage that repair and recovery turns out to be impossible even after removal of the focus Finally it should not be forgotten that causes other than allergic ones may be partly or alone responsible for the diseases in question

There exist statistics showing the favorable effect of the removal of infection foci but other statistics too have been published which deny both its preventive and its curative effect These statistics are open to *considerable criticism* Thus *it is illogical to compare the group of* operated cases with the group of unoperated ones and to state that the percentage of attacks is equal in both groups For the former group naturally comprises the most serious cases as well as those in which a focus has produced chronic intoxication and ensitization for a long time but in which the symptoms had not yet become manifest These after all are the patients with local and general symptoms of infection In such cases it is even possible for the first attack to occur directly after the removal of a focus This fact is then used—wrongly in my opinion—as a powerful argument against operating whereas it is to a much greater degree an indication of the causal connection between the focus and the systemic disease Such a post operative attack, however should be prevented by performing the operation under protection of antibiotics

Focal infection and asthma

The number of asthma patients in whom the first attack followed upon an infection of the respiratory passages is considerable This fact alone already points to the connection between bacteria and asthma If there are patients in whom a non allergic bacterial toxaemia may be assumed to be the cause of their attacks is doubtful But if we assume also here the existence of allergic sensitization by bacterial products and apply our knowledge concerning these products the focus theory assumes a different aspect For in asthma as in arthritis the chief objections against this theory were that (*a*) removal of a focus often turned out unsuccessful and that conversely (*b*) there may be attacks in the absence of a demonstrable focus Harley pointed out that it is impossible in some cases to do away completely with a focus but that the principal reason for this failure must be sought in the non specificity of the nucleo-proteins When for *instance* a *streptococcal focus in the tonsils* which has caused the sensitization is removed it is possible for re absorption of nucleo proteins maybe of another group to continue from another place for example from the nasopharynx This is one explanation based on the non specific Shwartzmann phenomenon

Recent investigations have shown that probably it is not so much the bacteria in the patient s infection focus that constitute the danger to him, but rather the foreign groups with which he is infected Quite possibly in such an acute new infection the re absorption is more intense than from an old closed up focus

A recent objection against the focus theory is that the antibiotics capable of sterilizing the body fail to cure this bacterial sensitization and stop the attacks As against this one may argue that (*a*) sensitization is an existing condition which is not changed by antibiotics (*b*) re absorption of dead bacteria can continue for an indefinitely long time (*c*) re infection is a rapid process and (*d*) an allergic reaction may persist during a considerable time after the initial action of the allergen An example of this is that of the contact dermatitis

Indications for operation of focal infections

In asthma patients as well as in every other condition chronic infections should be carefully looked for In asthma infections of the nose the nasal sinuses the tonsils and the throat are frequently present The infections may be either the cause of asthma or only an aggravating factor For if during asthma the bronchi are sensitized to bacterial proteins the inflow of infected material from the upper air passages may provoke local reactions Such reactions may be compared to the phenomenon of Arthus or Pirquet s reaction Here the result will be chronic irritation rather than the occurrence of attacks Especially the post nasal drip has a bad reputation in this respect

A careful selection of cases that are to be operated on is necessary In some cases a preliminary desensitization is preferable in order to increase the patient s immunity If the patient suffers from nose obstruction by nasal polyps or other reasons suffers from a purulent sinusitis or repeated attacks of tonsillitis he should be operated on under antibiotic and spasmolytic protection In such cases the indications for operation are essentially the same as in patients who are not allergic

In addition one must bear in mind that the absence of a visible focus thus of inflamed tissue does not by any means imply that no focus exists To trace it is the task of the bacteriologist and to suspect it is the task of an accurate clinical observation of the patient

References

BILLINGS F *Focal infection* The Lane Medical Lectures New York, D Appleton & Co 1918
BOLCK, F ARNDT J *Virchow s Arch 324* and *325* 1954
HARLEY D *Progress in Allergy III* S Karger Basel 1952
LANCEFIELD R. *Harvey Lect res 1940/1941* p 256
PAGEL, W *Progress in Allergy I* S Karger Basel 1939
STETSON C A *Symposium in Rheumatic Fever* University of Minnesota Press 1952
THOMAS L *Symposium in Rheumatic Fever* University of Minnesota Press 1952

ROLE AND TREATMENT OF INFECTION OF THE UPPER RESPIRATORY TRACT IN ASTHMA*

by

J TABART

The high incidence of rhinopharyngeal and dental infections associated with the asthmatic disease was shown off after the improvement of investigation methods (X rays lipiododiagnosis) Various aetiological hypotheses were suggested in this respect is infection a cause of asthma or only a superadded cause? is infections asthma of allergic origin or not?

We confined the quotation of the works issued for the last 25 years to those dealing with rhinopathies and particularly sinusites Our experience being scarce as regards dental infections we cannot give any conclusive view on this subject

I STATISTICS

In U S A Cooke and Grove [1] [1] in 1933 reported 49 per cent of asthma cases provoked by various infections of the rhino pharynx out of a series of 688 cases Incidence for sinusitis only was 39 per cent in asthmatics aged from 10 to 30 years 65 per cent in asthmatics aged 30 to 50 and 83 per cent in those over 50 years Kern and Shenk [2] out of 400 asthmatics found 70 per cent sinusitis clinically and radiologically confirmed Kelley also [3] in 1936 valued 89 per cent of asthmatics as bearers of sinusitis in a series of 100 cases Chobot [4] [5] out of 88 asthmatic children under 15 years age found 67 per cent sinusitis Reversely Bullen [6] studying the various associated symptoms and signs in 400 bearers of sinusitis admitted to Rochester Hospital valued only 25 per cent chronic non tuberculous pulmonary affections of which a half were asthma As for Bivings [7] in 1940 asthmatic bronchitis is always related to an infection of the upper air passages it was present in 35 per cent of 235 children showing upper respiratory infection

In Europe Haibe of Liège [8] in 1932 out of 1 000 asthmatics found 50 per cent of cases provoked by seasonal rhinobronchitis 25 per cent by bronchial infection 0 5 per cent by sinusitis

In 1940 Broerson of Copenhagen [9] holds that out of 435 asthmatics 292 are bearers of nasal anomalies Jacquelin and Chait [10] of Paris in 1936 out of 430 asthmatics followed up for from 4 to 6 years found a diseased condition of the nose in 114 Valin of Mont Dore [11] out of

* From Hôpital Bichat Paris (Prof T J G Turiaf)

673 asthmatics quoted 60 per cent presenting nasal lesions In England according to Bourne [1] asthma subsequent to nasal lesions is very common and gets much relief from surgical operation At the Mont Dore Congress 1950 Rebattu and Mounierkuhn, [13] reporting on the relation of asthma to the upper air passages emphasize the high incidence of acute or chronic sinusitis hypertrophic chronic rhinitis of infective origin ($^1/_3$ of cases) and the usual presence of rhinopathies of allergic origin ($^1/_3$ of the asthma cases) Mariano Castex [14] then Rossier [15] quote asthmatic manifestations occuring after infection of the respiratory tract

Quite recently Wilken Jensen [16] in 1951 in Copenhagen finds out of 512 asthmatic children 225 bearers of rhinopathies of which 65 with sinusitis The same year Kourilsky [17] studying very carefully 28 asthmatics could demonstrate in 20 of them the presence of microbial pathologic changes of the upper respiratory tract bilateral maxillary sinusitis 44 4 per cent maxillary and frontal sinusitis 27 7 per cent unilateral maxillary sinusitis 16 6 per cent unilateral frontal sinusitis 11 1 per cent

II NASO SINUSAL ALLERGY

From the whole of such works it appears that the association of nasal and asthmatic manifestations is a matter of fact It suggests necessarily the possibility of common reaction symptoms at the different levels of the respiratory mucous membrane Our concept of asthma is indeed one of a neuro vasomotor rhino tracheo bronchopathy developing through a dual general process an inflammatory and secretory defect of vaso motor origin and a bronchomotor defect The ultimate phases of the process ends in obstruction of the bronchioles at the level of the lower air passages which obstruction promotes dyspnoea In the upper tract the oedema and hypersecretion express the different phases of the naso sinusal allergy which have been well described by Bourdial Andre and Clerc [18]

In the initial stage of acute allergy only is oedema of the naso sinusal mucosa clinically and radiologically detectable during the attack (in 85 per cent of cases according to the American authors) In this stage between the attacks the mucosa resumes entirely its previous structure

To an aggravated stage (from repetition of the paroxysms) does correspond the serous allergic sinusitis the distended and infiltrated mucous membrane becomes thickened radiography confirms its permanent and non reversible involvement Occasionally the presence of minor polypi of the middle meatus and of eosinophilia in the secreta is recognizable

In an ultimate stage the mucosa of the sinus becomes proliferant that is polypous allergic sinusitis as proven by bilaterality of the lesions absence of purulent secreta anosmia

It is remarkable that the manifestations are sometimes localized on a story of the respiratory tract sometimes generalized to all respiratory mucosae from the finest bronchial ramifications up to the beginning of the nasal mucosa

III VARIOUS ASPECTS OF THE INFECTION IN ASTHMA

Under such conditions one may wonder to what extent such a microbial aggression as previously localized on the mucosa of the upper respiratory tract is susceptible of promoting asthmatic manifestations in those forms where allergy and nasal infections get associated one wonders which is the prior predominant factor

a) *Infection as a primary factor of asthmatic manifestations*

This is the view of Cooke[19, 20, 1] who within a 10 year experience could observe that in children there is in many cases a history of acute infections such as whooping-cough measles pneumonia influenza followed after several months by a recurrent bronchitis which finally will assume an obvious asthmatic character Such diseases leave behind them some infection foci or some secondary invaders which in their turn become primary causes of asthmatic allergy Until 5 year age these foci are placed in the lymphoid tissue of the tonsils pharynx and naso pharynx Following the development of paranasal sinus the infection localizes itself fairly often in this cavities The most commonly responsible bacteria are according to Cooke[20] pneumococcus hemolytic and non hemolytic streptococcus microcatarrhalis streptococcus viridans

It is also the view of Kourilsky and co workers that infection is not to be seen only in old standing or inveterate asthma Bronchial infection occurs long before the outbreak of the initial asthmatic manifestations or is often concurrent with them Search for the cause of descending infection should be systematically made at the level of the sinuses and teeth Deep focal infection may be invisible exteriorly (sinusitis tonsillar granuloma) surface infection may be overlooked (purulent rhinitis infection of the gums and interdental lingulae) Best prophylaxis of asthma according to Kourilsky[2] consists in removing the infective foci (operation on sinus punctures cleansings antibiotics vaccinotherapy) The author s arguments and conclusions[2, 23] are consistent with those previously stated by Gallup[24] Frouchtman[25] Spoujitch[28] Stevens[27] Asthma takes rise from the meeting of infection and an indispensable favourable terrain

As for Jimenez Diaz [8, 29] the part of infection inbronchial asthma is very significant in most cases (82 per cent) In a very large proportion of cases its influence may be the actual causal factor in a lesser proportion the infection is added to other allergenic effects its development is encouraged by the alterations in structure and reaction of the tissues it comes to holding a prevalent role in the activations persistency and evolution of the asthmatic manifestations Jimenez Diaz considers the evolution as presenting three phases in the bronchial mucous membranes subsequently to the rhino-pharyngeal infections paroxystic phasis marked by a return to normal following each attack, pathergic phasis where Forbusoni s granulomatous inflammation may be noted reversibility of the symptoms being no longer observed finally the ultimate angiodermale phasis accompanied by deep changes fibrinoid degeneration of the collagen system granulomas periarteritis nodosa nephritis or hypertension Such an evolution is not unavoidable and may be stopped by an appropriate anti infective treatment (antibiotics and especially microbial vaccines)

b) *Infection as a significant but non preponderant factor of the asthmatic manifestations*

Williams and Williams of Cardiff [30] admit that infection of respiratory tract is but one of the numerous stimuli apt to establish the status of asthmatic diathesis They noted the presence of infection in 55 per cent of asthma cases which observation allowed them to conclude that the association infection asthma is not casual It seems to be one of the determining factors of the attacks but only in the proportion of 14 per cent of cases that is far less than the other stimuli dust allergy moulds alimentation emotional shock pregnancy menstruation climate fatigue Williams and Williams do not regard the infection of the air passages as holding a preponderant part in asthma

Rackemann [31, 3] claims that the infections of the respiratory tract either primary or secondary are significant in intrinsic asthma but that one cannot decide whether they are properly a direct aggravating cause or an effect among the physical causes (depletion) and the emotional psychosomatic causes

c) *Infection of the upper air passages as a factor of bronchial infection superadded to allergy*

That is the opinion expressed in U S A by Rinkel and Randolph [33] who consider the problem of infection as negligible once the allergies from food and inhalated substances were treated In France Jacquelin and Chait [10] observed as many improvements as negative results and aggravations in the course of treatment of 45 patients who had been operated on

from polypi sinusites or who had experienced punctures and cauterizations which demonstrates that there is not in all cases a causal connection between nasal infection and asthma J Sclafer[34] had the same opinion

Existence of bronchial superinfection in the asthmatic children and in inveterate asthmatics under the appearance of descending infections of the upper respiratory tract is wellknown and needs no further explanation here They constitute an episodic complication or a state of inveteracy which from the fact of their being anterior to or associated with asthma should not be considered a primary cause Besides it is well known that acute infections with high fever of the tonsils sinus middle ear may induce the same remissions of asthmatic manifestations as do acute infections of the lung for instance pneumonia But here do intervene other 'stress phenomena which may account for this effect

Considering the diversity of opinions on so complex a question one is led to assume that there is some process of interreaction between the rhino naso pharyngeal infections and the manifestations of asthma

IV POSSIBLE MODES OF ACTION OF THE INFECTION IN ASTHMA

a) *Nasal irritative thorn*

This is an assumption commonly put forward since it was formulated *by Bezançon and De Jong*[35] *in respect with asthmogenic pulmonary sclerosis* It has been stated that the changes in the nasal region were enough to discharge the manifestations of bronchial asthma in potential asthmatics As held by Leroux[36] the notion of irritative nasal thorn has been ill interpreted For discharging an attack of asthma a mere passive stenosis of the nose due to infection is not enough a deep lesion of the mucosa is necessary (oedematous ethmoid and its ending in polyposis inflammatory reactions of the same type as the underlying asthma) Rebattu and Mounierkuhn at the 11th Congress of Mont Dore[13] together with a number of other Congressists have confirmed the difficulties in interpreting such a process We think for our part that most of nasal polyposes in the asthmatic are wittnesses and not causative factors of asthma

The role of the endobronchial microbial thorn as maintained by focal infection of the upper respiratory tract is put forth by Haibe[8] [38] Kourilsky[23] Frouchtman[25] Haibe[8] was the first to call attention to the importance of nasal and pulmonary infections in the past history of the asthmatics They would leave a chronic infection whose responsible organisms would irritate the ends of the corresponding nerves and would sensitize the body to their toxins on an asthma predisposing terrain According to Haibe[3] the microbial nasal thorn would be

due to staphylococcus and the bronchial thorn to streptococcus Kourilsky [3] postulates that the irritative thorn is actually and materially constituted by the endobronchial infection infective involvement of the deep layer where the glands are situated as well in recent as in long standing asthma The infection plays a determining or revivifying role As for Frouchtman [25] the same circumscribed changes of the endo bronchi (sometimes latent therefore overlooked) maintain a condition of bronchial irritability Descending superinfections of the rhino pharynx provoke by reflex action local or remote bronchial spasms Such infections obligatorily promote inflammatory phenomena by bacterial allergy

b) *General microbial allergy*

Some authors suggest the possibility of a general process of microbial allergy the allergens originating from a focus of the upper tract

Previously held by Cooke [20] Brown [39] Walker [40] Thomas [41] Swine ford [4] [43] the assumption of bacterial allergy was maintained by Jimenez Diaz [9] and his pupils of whom Surinyach [44] at the last Euro pean Congress of Allergy Infection on the basis of a dysreactive constitutional disposition promotes the allergic reaction of the respira tory mucosa which develops from the state of transient acute oedema to the non reversible state of inflammation From comparison with his own observations on malignant abacterial endocarditis Jimenez Diaz suggests that the lesion of the vessels and connective tissue is the con sequence of the toxic effect of certain proteic fractions abnormal in quantity and quality as found in the plasma subsequently to the repeated aggressions of the bacterial allergens Among English authors Frank land [45] Harley [46] postulate the existence of an allergy specific to the organisms of the focal infection This reaction would occur in relation to the nucleoproteins and carbohydrates originating from the disinte gration of the bacteria conveyed by the blood into the sensitized territory

Stevens [27] postulates a process of bacterial allergy in the genesis of those asthma paroxysms which appears in children during a second phasis following a chilling On the one hand the asthmatic mani festations follow in frequency and intensity a curve parallel to that of the seasonal fluctuations of bacteria in the upper tract (maximal period from September to April) On the other hand the degree of cutaneous susceptibility to the nucleoproteins of these bacteria increases and decreases in a parallel fashion Stevens observed in those allergies by microbial sensitization a type of urticarial reactions the threshold of which varies 1/10—10 to 1/10—4 in normal children or in those subjects with only seasonal infections the reaction is always erythematous or of a delayed type the cuti positivity threshold of which is always below 10—4

c) *Acute infections of the respiratory tract as an intermediate factor to asthma*

Spoujitch [26] suggests that in addition to cases of sensitization to microbial allergens there are cases where bacteria act as factors encouraging the allergic or microbial allergic process (descending bronchitis opening the door to the penetration of exogenous allergens) Out of the infection periods the same subjects exposed to the same allergens do not feel any asthmatic disturbance when they were cured from their infection the asthma does not recur Other authors (Harley) [46] admitted that a focal infection may lower the threshold of the respiratory mucosa to the allergens brought in by the blood stream (bacterial) or by allergic load (Duchaine) [65]

d) *Infections of the upper tract as intrinsic factors of asthma*

Chobot [4 5] Bivings [7] Stevens [27] pointed out in children the frequency of asthma manifestations just concurrent with chillings by acute bronchio alveolitis leaving or not leaving residua for secondary re infections There is in this stage no properly called microbial sensitization and only does the irritability of the mucosa from the infection determine the obstructive inflammation of the bronchi In a more advanced stage the repetition of the infections subsequent to the predisposition to allergy or in the presence of the debility of the mucosae as pointed out by Flurin [47] Sergent [48] produce a certain degree of chronicity in the asthmatic manifestations As claimed by Salen [49 50] one deals with a vicious circle allergy predisposing to infection infection predisposing to allergic manifestations As for Williams and Williams [30] inflammation does not exert only a determining action on asthma it predisposes to the various specific or non specific stimuli such as wind fog vapour changes in temperature

In fact the question presents great complexity whichever the pathogenesis adopted the main argument as often evoked is that the removal of the infectious foci of the upper tract and of their remote effects is followed by betterment in the asthma condition

Our personal opinion is that the slight or obvious involvement of the sinus is a constant phenomenon in asthmatics Whether a mere veil was observed by diaphanoscopy to be unilateral or bilateral or whether the opacity was more pronounced as confirmed by radiography such aspects express the presence of oedema and increased serous secretion an expression of allergic disease of the whole mucosa Sinusal infection and its descending extension is a trivial process induced by retention of the secretions due to the swelling of the mucosa in the cavities One may say that the trivial infection is an additional phenomenon It is not a cause of the properly called asthma for in spite of operations such as punc

tures drainage the asthmatic manifestations do persist, as do recur the rhinopharyngeal manifestations after a more or less long time

It is likely that the acute or dragging infection helps in the discharge as suggested by Spoutich [26] and Harley [48] or by weakening the immunologic defences of the system or by allergic load (although the question of specific microbial allergy is still difficult to demonstrate clinically)

It is certain that repeated and chronic infections with descending tendency encourage the organization of ectasiant and stenosant disorders so common in asthmatics [53] [54] Thus is any rhino microbial aggression a threat of aggravation and exacerbation of pre existent chronic infection

VI TREATMENT OF RHINO-PHARYNGEAL INFECTIONS IN ASTHMA

We think that therapeutically any dragging infection of the rhino pharynx should be treated with active but non irritant medications free from secondary allergic or vaso motor reactions

Against nasal obstruction (due to minor infection or association of infection and allergy) we advise minimal focal cares We disapprove of the use of galvanocautery or silver nitrate cauterisations applications or pulverizations of anesthetic or vaso constrictive mixtures such as Bonain s mixture mixture of aromatic sympathomimetic oils We only advocate spaced nasal instillations of antihistaminics (preferably fluid vehicles or neutral excipients of Carbowax, vaseline glycerin type) Instillations, pulverizations or sub mucosal infiltrations of hydrocortisone acetate are advisable in the cases of full impermeability of the nasal ventilation Their efficiency is dramatic but transitory Usual cares in most cases ameliorate those conditions maintaining the retention of the secretions in the closed cavities By setting up the drainage of the catarrh one causes the infection to clear up by itself

In the stage of acute or subacute rhino pharyngeal infection the use of antibiotics locally or systemically is indicated The choice of the antibiotic should be guided most often by the previous test of susceptibility of the organisms from the rhino pharyngeal secretions to the different antibiotics We make reserve as regards penicillin owing to its high allergisant potency Better and durable results may be expected from sulphamides but these are more easily tolerated by systemic route than by local route

In the cases of purulent sinusitis we prefer medical management decongestive inhalations of menthol alcohol at 4 per cent antibiotics aerosols (penicillin excluded) repeated punctures cleansings of the maxillary and ethmoidal sinuses by Proetz s method

Dilapidating surgical interventions (exposure of the maxillary sinus

with drainage by nasal counteropening curettage of the ethmoid) should be dissuaded in most cases of sinusitis in asthmatics Relapses after a certain length of time are not infrequent Tendency of the asthmatic evolution towards aggravation is more often the rule than generally believed We also disapprove of the other endo nasal surgical inter ventions resection of septum luxation and exeresis of turbinate etc Removal of polypi is only indicated in the case of big polypi causing a permanent defect to nasal aeration

Vaccinotherapy with stock vaccine or autovaccine from germs collected from the sinuses or post nasal spaces injected by intradermic or subcutaneous route has effected unquestionable sedations Prophylactic vaccination out of the infection periods should be performed with very low doses from 1000 to 100 000 germs per cc because of the hyper susceptibility of the patients to the bacteria utilized We had the oppor tunity of using autovaccines during infection periods Under these conditions the dosage had to be far more reduced still the scheme of utilization being similar to the methods of specific desensitization called coseasonal

Specific desensitizaton against dusts and moulds by neutralizing the chronic factors of oedema of the rhinopharyngeal mucosa has yielded gratifying results which may be compared with those obtained by Hansel [51 5]

Lastly the thermal sulfurous cures against the infection Luchon Cauterets Allevard the cures against the asthmatic terrain Mont Dore La Bourboule Saint Honore are prophylactically very beneficial against infections of the air passages in asthmatics especially with the use of thermal gas

Conclusions

1) Infection of the upper respiratory tract in asthmatic diseases is a very frequent phenomenon but its being anterior in time does not mean necessarily that its role is preeminent

2) The infection easily develops owing to the fragility caused by an increasing irritability of the whole respiratory mucosa of the asthmatic

3) The infection is occasionally a determining factor but usually an aggravating factor

4) It is essential to treat the nasal and sinusal infections Medical management is preferable to surgical procedures which are traumatisant and may be an aggravating factor of the asthmatic disease

5) Specific treatment of the microbial allergy has not yet given con clusive results in the asthmatic disease

References

1 Cooke et Grove *Arch Int Med 56* 779 octobre 1935
2 Kern et Shenk *Tract Arch* Otol *18* 425 1933
3 Kelley *Laryngoscope 46* 692 1936
4 Chobot *A M J Dis Childr 45* 25 1933
5 Chobot Uvitsky et Dundy *J of Allergy 22* 106—110 1951
6 Bullen *J Allergy 4* 40‸ 1933
7 Bivings *J A M A 115* 1434—5 26/10/40
8 Haibe *Bull Acad Nat Med Pa is 3* 107 474—8 1932
9 Broerson Acta Otolaryng Stockholm 20 p 373 1934
10 Jacquelin et Chait *Presse Medicale 44* 601—2 11/4/36
11 Valin *Soc d Otor Laryng Lyon* 12 juin 1937
12 Bourne *Brit Med J 2* 870—1 29/4/39
13 Rebattu et Mounierkuhn *2° Congres de l Asthme du Mont Dore* 1950
14 Mariano Castex *2 Congres de l Asthme du Mont Dore* 1950
15 Rossier *2° Congres de l Asthme du Mont Dore* 1950
16 Wilken Jensen *Acta Otola yngol supp 109* p 202—209 1953
17 Kourilsky R Kourilsky S et Mignot *Bull Acad Méd* janvier 1950
18 Bourdial Andre et Clerc *L Allergie naso-sinusielle* 1 volume l Expansion Scientifique Francaise 1951
19 Cooke Asthma in relation to Sinus Disease *T ans Am Climat & Clin Ass 93* 50 1934
20 — *I fective Asthma in Allergy in Theory and Practice* 1 volume Saunders Co 1947
21 — The importance of chronic sinusitis in the treatment of bronchial asthma *N Y State J Med 41* 455 1941
22 Kourilsky *Sem Méd des Hôp de Paris* p 3409 6/11/49 *Sem Hôp de Paris* p 4754 14/12/50
23 — *Jou nal f a ç de Médecine et de Chir Thor 5* 351—375 1951 *Ann de Medecine Tome 53* 195‸ N 2
24 Gallup *Paris Méd cal 105* 91—6 31/7/37
25 Frouchtman 2 Congrès Européen d Allergie Copenhague 1953 in *Acta Allergol*
26 Spoutich 2 Congrès Européen d Allergie Copenhague 1953 in *Acta Allergol*
27 Stevens et Gordon *Ann Allergy 8* 684 1950
Stevens *J Allergy 29* 221—6 1953
28 Jimenez Diaz *El Asthma y Affeciones afines* Madrid 1953
29 — 2 Congrès Européen d Allergie Copenhague 1953 dans *Acta Allergol supp III* 105—142 1953
30 Williams et Williams *Brit Med J II* 897 22/10/49
31 Rackemann *Clinical Alle gy* New York 1931
32 — *2° Congres de l Asthme* 1951 *J.A M.A 142* N 8 334—337 25/2/50
33 Rinkel et Randolph *Food Allergy* 1950
34 J Sclafer Communicat on personnelle
35 Bezançon et De Jong *P esse Médicale* 8 décembre 1920
36 Leroux *L Hôpital 24* 679—681 1936
37 Haibe *Bull Acad Nat Méd Paris 3* 107 474—478 1932
38 — *Bull Acad Nat Méd Paris 3* 108 1454—9 1932
39 Brown *South Med J 27* 856 1934
40 Walker *A ch Int Méd 43* 4 9 1929
41 Thomas *Asthma its diagnostic and t eatment* Ed P Hoeber 19‸8
42 Swineford et Hollman *J Allergy 18* 196 1947
43 Swineford et coll — Studies in bacterial Allergy *J Allergy Vol 26* N 2 1955
44 Surinyach Oller *Ann Méd Ba celona 35* 321—9 sept 1948
45 Frankland *Practitioner*

46 HARLEY *Prog ess in Allergy vol III*
47 FLURIN *Bull Méd Soc Méd Hôp Pa is* 5 mai 19.2
48 SERGENT Les rhino-bronchites descendantes *Les G ands symptômes respirato res* Doin Paris 19.4
49 SALEN *Acta Allerg* 127 66 1948 179 83 1948
50 — *2e Congres international de l Asthme du Mont Dore* 1950 465
51 HANSEL *Alle gy of the Nose and pa anasal S nuses* St Louis Mosby Cº 1936
52 — Nose and Sinuses *J All gy* 1 43 1929
53 TURIAF BLANCHON CABAIL *Sem des Hôp* 6 p 1846 1950
54 TURIAF MARLAND ROSE *Sem des Hôp* 28 N 74 p 2993
55 DUCHAINE *2e Cong es de l Asthma du Mont Do e* 1950
56 VAUGHAN *Practice of Allergy* Saunders.

occasions in the case of intrabronchial foreign bodies and benign and malignant tumours of the trachea

b) It is true that in this group a clear clinical picture of bronchial asthma is observed but further bronchological examination shows anatomic anomalies of the bronchial tree In this case we usually find anomalies in the form of a bronchial cyst or bronchiectases etc

It is still quite uncertain whether the bronchial asthma is caused by these anomalies or whether the two diseases result from a particular constitution We hold the view that in cases where anatomic anomalies are found an attempt should be made to cure these anatomic anomalies Such diseases constitute a constant source of danger on account of recurring infection haemoptyses etc We observed several cases of bronchial asthma in conjunction with serious infection of the bronchial mucous membrane After treating this infection we usually saw a marked improvement of the bronchial asthma This is quite the opposite of the assumption that an infection would produce stress reaction thereby reducing or removing the bronchospasm We observed in a number of cases that surgical treatment of bronchiectases or bronchial cysts led to a marked improvement or cure of bronchial asthma

SUMMARY

1) It is essential that every patient suffering from the serious syndrome of bronchial asthma should be subjected to a complete examination A complete examination of bronchial asthma should also include bronchological examination as an important feature in addition to a clinical and allergic examination Lung function examination is also very important

2) Pseudo asthmatic conditions are frequently observed in bronchial diseases in conjunction with bronchostenosis

3) The clinical picture of bronchial asthma is observed in conjunction with chronic bronchial infection on the bottom of bronchiectases or bronchial cysts In this case resection therapy can sometimes give excellent results not only as regards the removal of the infection but also the disappearance of bronchial asthma

DISCUSSION

R ALEMANY VALL

Though the surgical treatment of asthma is empiric we think that we should not disregard it because with this we can obtain a disappearance of the crises for a rather long time

We want to speak here of the extirpation of the second and third pair of dorsal ganglia or the resection of all the nerves of the plexus hiliarus except the trunk of the pneumogastricus and of the recurrents With the first operation done by Prof Piulachs we have obtained some good lasting results for more than a year with an inveterate asthmatic whose case we could not get improved by any means The second operation (resection of the nerves of the flexus hiliarus at first uni lateral later on bilateral) was done by Dr Margarit a thorax surgeon

This operation has enabled us to see easily all the organs of the area because they were surrounded by very few adipose tissue

These operations are delicate particularly those which are concerned with the anaesthesia

This anaesthesia must be perfect executed with the most modern instruments because the bronchial contraction only ceases with great difficulty These patients are only bronchial asthma patients without other lesions (bronchiectasis car cinoma tuberculosis etc)

THERAPY OF EMPHYSEMA

An Abstract

by

N G M ORIE

It is very difficult to give any summarizing article on therapy because the point in therapy is the details of its application and the details of the situations in which the different possibilities have to be applied It is even more difficult to discuss the therapy of disease of which the basic mechanism is not understood

The fact that the treatment of emphysema has been included in this symposium on asthma indicates that both diseases are considered more or less identical

I am inclined to agree with that point of view It implies that obstructive emphysema is a result of bronchial obstruction which is in the majority of cases of asthmatic origin I would even go further and suggest that most of the other lung diseases in themselves are unable to produce emphysema

That means that if emphysema is met with e g in tuberculosis in sarcoidosis or in bronchiogenic carcinoma it is not related to that disease but it is the result of an independent asthma existing simultaneously with the tuberculosis sarcoidosis or carcinoma [1]

This can only be proven by family history and by allergic phenomena existing with certainty before the disease in question

Witkop has given some very clear data on sarcoidosis

We have some similar observations in tuberculosis (De Vries)

Distension of the lung does not give the functional pattern of emphysema

If the foregoing is true every case of emphysema will show

a) a certain degree of asthma

b) a certain degree of irreversible anatomical change being the effect of the asthma

We do not know the exact relations between the two components Sometimes next to these two features which are always present

c) a complicating infection and in those cases we are often dealing with overburdening of the right heart cor pulmonale

[1] We have stressed elsewhere that the situation is different in so-called idiopathic bronchiectasis when we consider the asthma as a causative factor

It cannot be excluded that a simultaneously existing asthma alters the course of the disease in the other groups

In using the term asthma we use it in the broad sense allergic (?) expiratory embarrassment on a constitutional base often without clearcut attacks (see Israëls)

All this means that there is a fluid transition between asthma and emphysema Most of all in older age groups where the anatomical effects as a rule are more pronounced

As a matter of fact there is no sharp distinction between old age asthma and emphysema although there are cases in which the asthmatic factor or the anatomical pathology is but little pronounced

Therapy

Which are the therapeutic possibilities of emphysema?

Unless we know the cause of asthma we have no etiological therapy The conclusion from the foregoing is clearly that to a large extent the therapy of emphysema goes together with the therapy of old age asthma but even the problem of the therapy of old age asthma would be too extensive to treat in a few pages

We therefore will give only a few summarizing remarks mainly in relation to our own experiences

Symptomatic treatment

Treatment of complications

A) Infection (which is present in only a minority of the cases although patients with emphysema show a strongly marked tendency towards bronchial infection)

We have not to go into details on the antibiotic therapy of infections which would be far beyond the scope of this paper We can only point out that in the chronic infections Haemophilus influenzae usually is the infecting agent whereas in acute infections usually pneumococci are found Adequate antibiotic treatment follows from the etiologic agent and from the sensitivity of that agent towards the antibiotics

It must be mentioned however that in chronic cases most of all in this older age group the danger of increase of asthmatic symptoms after a successful antibiotic therapy is far from imaginary

Severe even fatal exacerbation of asthma after successful antibiotic therapy occurs only occasionally usually the beneficial local effects of the therapy are predominent

The possibility of the incidence of severe reactions is no reason to omit antibiotic therapy but it may be a reason for follow up with ACTH therapy if the asthma is more predominant after the treatment

B) Right heart failure—oxygen therapy

A second complication which may need therapy is a burdening of the right heart or straightforward right heart failure

In uncomplicated emphysema (unless in terminal stages) there is no

marked hypoxia and therefore there is no burdening of the right heart to a considerable degree

Severe hypoxia in emphysema means infection in 99 out of 100 cases Once in a while a severe asthmatic attack or severe diffusion disturbance has the same effect

In that case hypoxia calls for oxygen therapy and at the same time right heart failure is impending

In infected cases of emphysema with burdening of the lesser circulation this type of therapy is necessary

It includes *antibiotic therapy* as a most important measure and next symptomatically cardiac stimulant drugs
bronchodilators
O_2

The latter however may be a dangerous medication in depressing the ventilation It has to be applied with the utmost care and sometimes additional measures (stimulation of the central nervous system or artificial respiration) are necessary

Treatment regarding the anatomical change

Pneumoperitoneum

Literature on this subject is confused

Improvement of diaphragma movement is frequently seen but not apparent from function tests

One may visualize that the improvement of the diaphragmatic movement is counterbalanced by the unfavourable influence on the cheque valve mechanism which increases its effects when the lung is brought from strongly inspiratory into an expiratory position

Our own experience is disappointing with once in a while a successful case Barach states that in good cases the venous pressure falls on induction of pneumoperitoneum

Maybe the choice of patients will be easier if the methods of measuring the elastic and viscous properties of the lung are simplified

Our actual experience with these methods is too limited to draw any definite conclusion

Therapy of the asthmatic factor itself

Anti allergic therapy

Positive skin and inhalation tests are much less frequently seen in this (older age) type asthma then in the younger groups We therefore think that specific desensitization less often takes part in emphysema therapy than it does in younger individuals

Symptomatic drug therapy
Because this has been discussed by the other lecturers I think I may only mention the points of interest for the emphysematous patients

Generally speaking the drug therapy does not differ significantly from that in asthma in general

There are however a few exceptions

Atropine like substances in our experience give better results in the older age groups (with less allergy?) than in the young patients (with pronounced allergy)

Anticholinergic antihistaminics act very favourably in both groups The mode of action of aminophylline is neither understood in young nor in older age groups

ACTH—Cortisone
Our therapeutic results demonstrate that ACTH (and Cortisone?) is much more effective in older people than in young ones

This is in accordance with the fact that strong allergic reactions cannot be handled with ACTH and on the other hand that this type of allergy is uncommon in the older patients Dr Ten Cate has given you a number of examples of the results of ACTH in younger and older patients

If we accept that the development of asthma and emphysema in older people is largely dependant on disturbances of normal pituitary adrenal reactions (which is hypothetical) we can much more easily understand the good results of ACTH particularly in this group and at the same time we can easier accept the fact that as a rule this therapy has to be continued once we have started it

Fever therapy
S oil—typhoid vaccin

This implies that this type of ACTH substitute therapy is effective once in a while and at the same time that these results are seldom lasting

Some protracted effect is met with however in a number of cases (because here the lack of autogenous Cortisone is not substituted but the endogenous production is—temporarely—stimulated?)

SUMMARY

Summarizing I may say that from a practical point of view antibiotic therapy is sometimes useful if an infection is present It has however to be kept in mind that particularly in this group the elimination of the stress due to the infection may be very harmful and even fatal

Desensitization is not often used in treatment of emphysema Maybe in these cases parts of its result are aspecific (baterial vaccines)

Pneumoperitoneum has been disappointing but offers successful treatment once in a while

Symptomatic drugs are useful anticholinergic substances and anti cholinergic antihistamines have provided useful additional help most of all in the older group Their effect in the protection test is clearcut

ACTH has its best indication in this group of older people It has to be continued however in an effective dose

Stimulation of the pituitary adrenal system therefore offers not seldom temporary benefit

Psychotherapy We have insufficient data in this type of treatment I could not help introducing a certain amount of a speculation and conjecture in this paper

I apologize—and I am fully aware of the necessity of doing so—but I may add that the approach to therapy of any type of asthma is hardly possible from a purely factual point of view

I sincerely do hope that this situation will change as soon as possible and that our efforts may contribute to the realization of this area of asthmatherapy

References

A few papers in which data are given concerning *our own* experiences in this field, are

Asthma bronchiale etterige (bacteriële) bronchitis en het endocrine systeem (Bronchial asthma purulent (bacterial) bronchitis and the endocrine system) Thesis A. A. ISRAËLS Groningen 1952

Longfuncties na longresectie (Lungfunctions after lungresection) Thesis E E M GEELEN Groningen 1953

Onderzoek bij asthmapatiënten naar overgevoeligheid voor verstoven allergeenextracten (Investigation in asthmatic patients of hypersensitivity for aerosolized allergenic extracts Thesis H J TEN CATE Groningen 1954

Thesis H J SLUITER in press

Relation entre bronchiectasie et allergie by N G M ORIE E HUIZINGA A A ISRAËLS E E M GEELEN H J SLUITER and R WARRINGA in *Les Bronches vol V* 1955 No 2

Resection in bronchiectasis in press

Le rôle de la tuberculose et des infections non tuberculeuses dans le developpement de l in suffisance cardiaque droite by N G M ORIE F S P VAN BUCHEM H J SLUITER and A J F DE VRIES in *Acta Cardiologica T IX* 1954 No 4

DISCUSSION

TREATMENT OF EMPHYSEMA

by

BOEN SWINNY

The treatment of emphysema falls into five parts

1) *Study of the patient* 20 per cent of moderate and advanced emphysemas will benefit somewhat from the elimination of allergens and/or hyposensitization All emphysemas deserve allergic investigation because one cannot tell from history or other observation whether or not allergy might play a part in the individual under study In addition to this study the patient deserves to have careful repeated studies made of sputum for infection both by plating and by culture Radiography and vital capacity studies should be done Vital capacity should be done both before and after the use of bronchodilator such as isuprel as often this gives us an indication of prognosis

2) *Bronchial hygiene* This falls into two parts

a) Keeping the bronchial secretions as thin and watery as possible in order to wash out plugs and tenacious secretion by the use of expectorants Iodides especially potassium iodide orally or in combination with broncho dilators serve this purpose

b) Keeping the bronchial secretion free of infection by use of vaccines anti biotics oral parenteral or by aerosols the latter are to be preferred as there is the additional value of being able to combine the liquefying agents such as Alevaire with a bronchodilator such as isuprel

3) *Drug therapy* Bronchodilators such as ephedrine orally or the use of hand sprays containing epinephrine or isuprel Decrease in excess body fluids by Diamox or by digitalis often is helpful

4) *Physiotherapy* Teach the patient deep breathing exercises especially with emphasis on expiration while raising the diaphragma by tightening the belly muscles Bottle blowing or intermittent positive pressure is often helpful Patients in my experience will not tolerate emphysema belts

5) *General health* Reduce excessive weight to normal or slightly below normal Usually prohibiting smoking is helpful Watch out for anemia because the patient that has the normal blood count breathes easier than the one who has a decreased red count and hemoglobin Focal infections should be cleared up A well balanced diet with a light evening meal often helps the patient rest better at night

A CRITICAL REVIEW OF THE STATISTICS OF ASTHMA THERAPY

by

A HEYMER

The theme of this very interesting meeting is the therapy of asthma bronchiale The possibilities of the treatment of this illness have been dealt with thoroughly by the individual speakers in the course of this meeting They began with a view of the patho physiology of the asth matic attack and continued with the specific and non specific desensiti zation the vaccine therapy diet psycho therapy the physical and hor monal treatment and also the anti infectious therapy The gentleman speaking before me has given a critical view of these kinds of asthma therapy

Now there remains the task for me being the last speaker, to give a critical report of the statistics of the success of asthma therapy There will be not enough time to speak of individual publications not even to discuss groups of individual kinds of treatments Also I would most likely trouble you too much with this now at the close of this meeting Therefore I shall take pains to deal with some points which are important for the evaluation of the successful treatment of asthma I think these *points are important for the development of asthma therapy in general* I shall base my argument mainly on the teaching about the methods of the therapeutic clinical research of my highly esteemed teacher Paul Martini

For the evaluation of the success of asthma therapy the same rules have to hold basically as for all other diseases However we must admit that there exist especially great difficulties in the case of asthma bronchiale Up till recently the clinical picture of asthma bronchiale was not a very uniform one I should like to omit the psychogenic asthma in the following exposition and I should like to centre on the purely allergic asthma I admit that in all most every clinical picture of asthma there are psychogenic factors and I include the case in which e g the limit of tolerance towards allergens has been lowered through a psychial trauma so much that a genuine allergic asthma originates If one wants to evaluate the therapeutical success of such a clinical picture in which many factors partly of immense number play a role one often is confronted with insurmountable difficulties One has to exclude those cases of sickness in which asthma is merely a concomitant symptom as it may be the case in bronchiectasis silicosis Boeck s sarcoid

emphysema together with chronic bronchitis et al In the following exposition only the true asthma bronchiale caused by allergy is meant This clinical picture too is various In one case it appears in the form of severest attacks in other cases of dyspnoea which never quite disappears continues in between the individual attacks Then there are other clinical pictures in which a dry bronchitis continues to exist From this one will understand that the therapeutic possibilities of influence too are different in each case An evaluation becomes more difficult yet if other diseases are present simultaneously or if irreversible subsequent phenomena have appeared e g emphysema or an injury of the right heart Martini had to admit that it is hardly possible to test a *collective group of asthma patients* according to the principal of therapeutical comparison The *individual patient* therefore needs to be observed very closely during the course of his disease in which individual periods of his disease are to be compared If the patient is willing to stay hospitalized over a sufficiently long period of time there is the possibility to have a preliminary period of observation a therapeutical observation and a final observation The test is of higher value if there is the possibility to conduct several periods of observation and to compare these The result of this study still increases in value if one succeeds in carrying through a reversible test with a medicament i e after giving the medicine the symptoms of asthma disappear they reappear after the discontinuation of the remedy and remain during the giving of a pseudo remedy they disappear again at the renewed giving of the genuine remedy although the patient is unaware of this

Which signs does asthma bronchiale have that point to a therapeutical influence? They are rather numerous Subjective statements may be of importance There is the danger of course that psychogenic influence play a part in this The most impressive sign is the asthmatic attack Its characteristics are its severeness its repeated appearance and its more or less long intervals without trouble and symptoms There exists a possibility of evaluating the asthmatic attack objectively in regard to its patho physiological results which shall be dealt with below Clinical factors which point to asthma bronchiale and its capability of being influenced therapeutically are the physical state of the lungs with dry bronchitis with phrenoptosis the position of inspiration of the thorax the measurable limitation of the respiratory movement of the eosinophilia in blood and sputum the amount of sputum and its content of mucus of Charcot Leyden s crystals and of Curschmann s spirals and with the forms of asthma caused by infection of the bacterial flora of the sputum its influence upon the circulation and in severe cases of cyanosis also Martini thinks that the most important signs of asthma bronchiale and of its severity are the kind of attack and its

frequency The requirement for a systematic test of remedies of an asthma patient is an exact continuous registration of symptoms O Kuhne and H Martini have drawn up a scheme which they call asthma clock (Fig 1)

One can easily see that such a registration provides us with information about the remedies which would be useful in each individual case We have to add however that most of these medicaments act only symptomatically i e they remove or diminish those appearances which bring the cause of the disease to a head These individual observations provide no basis for conclusions as to asthma patients in general For this we need a tabulation of a large number of sick people which is subdivided into respective groups and of which we can see the efficiency of such a remedy The larger the number of patients who are therapeutically influenced the higher we can evaluate the therapeutical effect of this remedy One must not overlook the fact that asthma bronchiale is the result of complex processes The clinical picture which we find in the asthmatic attack is usually the result of allergic reactions which have developed over a long period of time up to this climax If the asthmatic attacks have occurred for years already changes in the anatomical substrate have mostly taken place changes which cannot be expected to be influenced by ordinary remedies for asthma From this we see however how difficult the evaluation of a therapeutic success of a remedy can be Hansen pointed out that one may not expect very much of a remedy for asthma that a final success can only be effected through a study of the causes Only this gives reason to expect a healing or preventing of asthma bronchiale

As was said above formerly we had to rely mostly upon the usual clinical symptoms in evaluating the success of the treatment of asthma bronchiale The study of the patho physiological change of respiration of the asthma patient have now given us several possibilities by means of which the results of a remedy upon the respiration can be checked more closely and more objectively A rough approximate estimate already permits a measuring of the apnoea and of the vital capacity More informative is a study with the aid of pneumotachygraphy We have tested our patients now for about 20 years by means of Fleisch s pneumotachygraph It permits to find out the respiration typical of asthmatic patients and also it shows any change during the therapeutic influence of a medicament as the following graph indicates (Fig 2)

We would think a normalization of the asthmatic patient to be due to a remedy if it comes to a chance of frequency of the minute volume of the time of exhalation of the maximum velocity and also of the proportion of medium to maximum velocity That can be seen in the graph

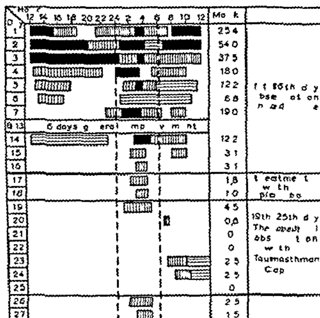


Fig 1

In the above scheme are registered the severe attacks the medium to slight attacks and merely troubled breathing They are registered for each day by hours Over a period of 27 days the appearance of the patient has been taken down in the time of preliminary observation during the pseudo treatment and during the therapy

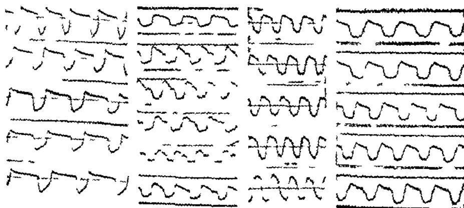


Fig 2

Knipping s apparatus in its modern form cannot be used in the case of an attack But often it can be used in an interval between attacks It provides us with excellent clues for the figures of the outer and inner respiration Further methods for the test of the function of the lungs especially in the case of an asthma patient have been dealt with in a monograph by Wyss They cover respiratory mechanics alveolar ventilation and the blood circulation in the lungs The complementary air respiratory volume supplemental air and residual air as well as the functional residual air during maximum ventilation is of importance For 2 years we have very successfully used Wyss and Hadorn s pneumometer in our clinic The apparatus is handy easy to operate and in repeated applications yields results which can easily be compared and which change in proportion to the betterment of the asthmatic condition It ought to be used today in asthma research The asthma patient shows a great decrease of the results of the pneumometer during the attack a slighter decrease in the latent condition The results constantly change during recovery because of therapeutic influence Similarly one can use the Tiffeneau test to determine the severity of an asthma case However the pneumometer is used in this case Wyss indicated methods as to the determining of the resistance of current in the bronchial system He also tried to use these in the evaluation of the severity of an asthma case

During the last years the possibility to get statistics of the success in asthma treatment with new means has become considerably better I regret to say that they have not been used accordingly by the authors who have dealt with this problem In many publications only general impressions are reported without stating this reason and what kind of therapeutical test had been used The number of those publications which survive criticism and from which truly convincing therapeutical conclusions may be drawn is very small For obvious reasons I cannot go into details about this The methods of therapeutical investigation are incomplete in many cases This is the reason for preventing us to hear with final certainty about many remedies in regard of their therapeutic effect although they are used daily on thousands of patients What do we know for instance about the success of the treatment with antihistamines Daily we read that their application promises assured success in the case of an asthmatic attack while a number of excellent researchers (Friebe et al) doubt any effect at all It would be a rewarding task to find out whether and how much we help the patient with antihistamines

Wyss rightly warns us to use new asthma remedies uncritically He demands they should be examined by way of an exact test of the function of the lungs He tested and compared aleudrin soluphyline and physio

logical salt solution in aerosol form He found that water or physiological salt solution have almost the same good effect as soluphyline which had been recommended highly until then in the form of aerosol Al though many authors already had proved in a number of tests that theophyllin in the form of aerosol is ineffective it is recommended again and again

Recently a renowned author maintained during a discussion that he could heal 95 per cent of asthma patients through psychotherapy I was surprised at this therapeutical optimism But I began to understand it a little when I realized that this statement was not supported by con vincing therapeutical investigations According to Martini however these should be demanded for the psychosomatic medicine and also for the psychotherapy of asthma bronchiale

FREE SUBJECTS

THE RELATION BETWEEN THE POLLEN FOUND IN THE SURROUNDINGS OF THE PATIENTS AND HIS ASTHMATIC CRISES

by

R ALEMANY VALL

During thirteen months we examined the pollen found daily (24 h) in the air of Barcelona collected in the Durham apparatus exposed on the terrace of the Municipal Hospital of Nra Sra de la Esperanza where the allergy service is established We have analysed a pollen coloured with fushina solution and examined it in its smallest details after being fully familiar with the pollen collected direct from a hundred different botani cal species We have also studied meteorologic conditions having in fluence on the deposit of pollen together with local and regional botani cal data morning rains clogged this deposit the afternoon and evening rains had a much lower effect in this respect Relative atmospheric humidity was the lowest between 11 a m and 2 p m —these were the hours where the largest quantities of pollen were dispersed here was a much larger number of pollens considered allergenic in March April and May months in which athmospheric humidity remained persistently the lowest

This preliminary study helped us to know the microclimate of pollinosis patients (24 h or 8 a m up to 4 p m or 4 p m up to 10 p m or 9 h next day)

Thus we succeeded in finding at times by means of the Durham appa ratus the pollen responsable for the condition such as the *Chenopodium* (about 28 elements) from 8 a m up to 4 p m on a four square centimeter surface of exposed slide the pollen of *Tilia argentea* abundant on the slides and proceeding from neighbouring plants on days when some patients had asthmatic crises the pollen of *Phitolaca dioica* in summer and at the beginning of autumn the pollen of *Parietaria officinalis* from 400 elements up to 10 in four square centimeters of slide exposed near the plants where the patients lived and according to their blooming times Far from these surroundings in town far from these plants the urticaceous plants did not reach a pollenproduction of 10 grains per 4 sq cm in May The gramineous plants had up to 20 pollens per 4 sq cm in Barcelona even in the central parts of the city in which no gramineous plants seemed to exist where however we have found *Poa annua* and *Millium multiflorum*

The pollen of *Platanus orientalis* found by us from 100 grains to 2000

graıns per 4 sq cm (Montserrat) accordıng to surroundıngs less abun dant or abundant wıth these plants

We have seen that there was a certaın relatıon between crıses and the quantıty of pollen the crıses occurred near the places where these plants were plentıful except perhaps the gramıneous

Barcelona has perhaps on account of ıts general geographıc con dıtıons protectıon agaınst wınds relatıvely hıgh temperature and hıghly varyıng humıdıty more pollens and spores of fungı on the exposed slıdes than places farther away from Barcelona havıng an open field more frequent wınds of greater ıntensıty and larger number of plants none of whıch are frequently found ın Barcelona

We have ıntended to establısh a classıficatıon of the spores found on the slıdes accordıng to theır sızes forms and colours even ıf such classıficatıon would forcıbly remaın ımperfect of the orıgın of the spores We thınk that such an orıentatıon would be suffıcıent for the physıcıan

1) The Ascomıcetı 2) The Macròsporıum type 3) The Alternarıa type 4) The Uredosporas 5) The Teleutospores 6) The Hemılthosporıum Sıncephalastrum Spondylcladıum 7) Hormodendrum and Cladosporıum 8) Large non classıfiable spores 9) Small non classıfiable spores

Round the end of sprıng summer and autumn there was a much larger quantıty of spores than ın wınter there were many days when we found 30 40 and more spores and on the other hand relatıvely few pollens

SPECIFIC TREATMENT OF ASTHMA

by

R ALEMANY VALL

The treatment by pollen is quite efficient at the early stages of the patho logic condition these stages are counted by seasonal years when only conjunctivitis or rhinitis are present Later when asthma appears —also of pollinic origin, although the whole picture may disappear specially in those sensitive to gramineous plants in those who are sensitive to other pollens a more or less seasonally evident rhinitis may remain present in spite of a specific treatment

In Barcelona we have patients sensitive to gramineous plants whose symptoms disappear even in the course of the same season if they are then subjected to the treatment but do not appear during the season if the preseasonal treatment has been followed

Patients sensitive to platanes suffer from rhinitis and asthma improve by the treatment although generally not quite so much as is the case with those sensitive to gramineous plants this occurs also in those sensitive to Parietaria officinalis of which many cases may be seen on the Mediterranea Coast this depends on the larger diffusion of pollen in the local ambient air of the patient in proportion to neighbouring plants When there is a large quantity of pollen present the treatment may even give less effects

We administer injections on alternate days or one every week or two weeks from one tenth to ten parts of 100—10 000 units for c c This specificity is the clearest and most evident of all allergic affections Cutaneous reactions remain positive even out of season—these reactions to certain pollens will reoccur even years afterward in patients without any crisis or very slightly affected (Parietaria) Those sensitive to cheno podium album respond very well to the treatment We found this pollen not only at the beginning of autumn but also in summer spring and even in winter

We have not seen pollinosis crises only appearing during the night we have seen however night crises in patients suffering from daily crises we have hardly seen any pollen in the houses of the patients and found a little at night on the slides

We saw cases sensitive to the pollens of Cosmos Aster Gladiolos Daisies etc in florists showing large cutaneous reactions and even focal reactions by simple scarification with pollen above them We do not advise a desensitizing treatment for these patients living in

contact with these plants and whose crises begin already in June

Those sensitive to both pollen and dust when the latter is wide spread in the ambient air of the patient but only in months of intensive pollen formation specially in Parietaria (April May or May June) must be treated only with pollen not with dust when these two months have passed the dust does not act any more although pollinosis crises may occur, less intensively, on account of there being less pollen

We have not often seen patients sensitive to hairs these always improve under treatment provided that the ambient air is not too full of hairs In our service of allergy in the Medical School the separation of various flour proteins was obtained (proteose globuline gliadine and wheat glutenine also albumin and rye globuline) which have been administered as diagnostic and therapeutic means for asthmatic bakers we have even obtained pseudopodic reactions in them, in general proteose and globuline were those substances which reacted most but the therapeutic results were relatively poor

THE USE OF GOLD SALTS IN BRONCHIAL ASTHMA*

by

LINO BUSINCO

A considerable number of serious difficulties prevent the formation of a clear pathogenic picture of bronchial asthma This illness which at first was interpreted as a simple manifestation of hypersensitivity in the bronchial area now appears to be dominated by a group of factors not all of which have been evaluated with any degree of precision Among those elements which accompany the simple allergic situation we must take into consideration the nervous dystonia the diathesis the circulatory disorder in the pulmonary area etc At times these pathogenic factors sum up with varying intensity one in regard to another or they interfere creating a mutating pathogenic background to the usual clinical manifestations of the asthmatic dyspnoea This uncertain situation engenders in practice the difficulty of controlling bronchial asthma with efficacious and decisive therapies

For several years among other medicines for the treatment of bronchial asthma we have been using a composition of gold salts (gold tri bromide and tetra bromide) associated with iodine arsenic and quinine (AM 49) Administered orally this compound has constantly given a good percentage of favourable results Out of 80 patients treated up until the present time we can show cures or notable improvements in 60 per cent slight improvement in 20 per cent and 20 per cent of failures The therapy is tolerated without difficulty and frequently has given surprising results even in severe cases Rascher Rieder Froesch Oehl Steinbacher Kleinsorge and other authors have reported similar results The favourable activity of gold salts on bronchial asthma has also been observed by Dudan Brunel Cans Jacquelin etc It is likely that this depends at least in part on an activity of the gold salts on the histiocytes operating as genetic antibodies As well as being located in the germinating centres of the lymphoid organs these histiocytes are also to be found near the walls of the capillaries so that they are readily accessible to the gold salts In support of this interpretation is the fact that during therapy with gold salts we have been able to observe contemporaneously with the clinical improvement a decrease in the rate of the gamma globulins which are known to be vectors of antibodies This decrease may very probably be attributed to a lessened genetic activity on the part of the histiocytes damaged or disturbed by the gold salts When the proportion of antibodies is either absent or reduced the hyperergic reaction would thus be eliminated or at least mitigated

Institute of Medical Semeiology of the University of Rome

THE FREQUENCY OF BRONCHIAL INFECTION IN ASTHMA AND DESCRIPTION OF A METHOD FOR STERILE REMOVAL OF BRONCHIAL SECRETION*

by

HELGE COLLDAHL

When bronchial secretion is drawn up through a bronchoscope contamination with throat bacteria often occurs

If bronchial secretion was collected by introducing a sterile catheter through a tracheal tube after intravenous narcosis with Evipan and Scoline no contamination occurred in 90 per cent of examined cases

With the last mentioned investigational technic it could be shown that asthmatic patients when BSR is not elevated do not have bronchial infection oftener than patients with healthy lungs

Further it could be shown that patients with mucopurulent sputum often have no bronchial infection The appearance of sputum which in these cases is often rich in eosinofilic leucocytes is due in all probability to the allergic reaction in the bronchi

In the investigated material bronchial infection occurred in about 25 per cent of the asthmatic patients

* As this subject was recently published in detail in *Acta Allergologica VIII* 163 1955 by SVEN BERGMAN HELGE COLLDAHL and ERIC NILSSON only a short summary is given here

PORTUGUESE CRENOTHERAPY IN ASTHMA AND ALLERGIC DISEASES

by

MARIO DAMAS MORA

This address pretends only to call attention to the advantages of crenotherapeutic treatment as an adjuvant of anti allergic therapy and to remind you that Portugal is rich in mineral waters with properties similar to many others all over the world

By allergy is meant—according to Messini in the etymological sense of the word—any and every modification of the reactivity of the organism, including both the increase and the diminution of the reactive state and therefore anaphylaxis atopy (Coca) idiosyncrasy phylaxis and even acquired immunity (Billard)

How did this conception of allergy arise?

The result of Pasteur s work which confirmed the notion of the body accustoming itself to bacteria and their toxins and thereby warding off the danger of a future invasion on a large scale reminds one of the old story of King Mithridates, who fearing to be poisoned used to take minimum doses of poisons daily in order to become immunized against them Hence the centuries old term mithridatism for the phenomenon verified by the end of last century and later on corroborated by the utilization on a large scale of sera and vaccines as a more efficacious means of guarding against various diseases

With the same idea in mind Prince Albert I of Monaco being very keen on marine biology engaged two French biologists Charles Richet and Paul Portier to find out the effect of repeated doses of poison from a marine animal *Physalia* (commonly called the galley or marine lung) on animals in the laboratory which he had installed in his yacht Princess Alice II

On returning to the laboratory of the Faculty of Medicine of Paris the two investigators replaced the Physalia by *Actinea* a sea anemone the poisonous extract of which, actinotoxin came to be used in the immunity experiments

A dog — called Neptune in memory of the two scientists sea voyages —was injected with 0 05 cc of actinotoxin per kg bodyweight on January 14 1902 An hour after this injection the animal was perfectly fit Four days later the same dose was repeated with identical result The animal kept perfectly bright until February 10 healthy happy active with a glossy coat —thus the report of the Academy of Medicine

On the latter day—write the two scientists—at 2 o clock in the afternoon we injected 0 12 cc of the toxin per kg bodyweight This at once produced vomiting defective action tremors of the front legs The dog lay down on one side completely lost consciousness and died half an hour later suffocated under the influence of this injection which given for the first time in this percentage to another unsensitized dog provoked only some sneezing and itching

These facts—they continue—removed all doubt we might yet have had not only are animals repeatedly injected with weak doses of toxins not immunized relatively to those injected for the first time they even appear to have been sensitized

This newly discovered phenomenon we call *anaphylaxis* Its revelation to a scientific world until then blindly credulous of the idea of small doses of serum or vaccines immunizing the organism completely altered the existing axiomatic notions and constituted as Arnault Tzanck declared one of the most notable milestones in modern medical science

Richet s and Portier s communication was followed by subsequent resounding confirmation Thus Arthus discovered that the anaphylactic shock can be provoked by a simple trivial injection of serum that intradermic injection of this serum can set up a kind of phlegmon—true local anaphylaxis (phenomenon of Arthus) and Nicolle in 1906 verified that if one prepares an animal with a first injection and injects its blood into another non prepared animal the latter in its turn becomes sensitive to a second injection

On the basis of these experiments Von Pirquet explained that the human body when in contact with any substance (dust chemical products foods micro organisms etc) may under certain circumstances react in a different way from the habitual one and that this sensitivity may originate the disease He called the sensitizing substance Allergen and the mutation in the organic reactions Allergia

Once this phenomenon was verified there occurred an entire series of surprises Sanarelli in 1924 prepared a rabbit with a non lethal injection of some microbe The following day he injected another microbial substance harmless to any non prepared animal and the rabbit died after a few hours with congestion and general haemorrhage completely unrelated to the injected products! Why? This reaction is inexplicable Whether general or local it will only occur with a short space of time between the two injections i e not more than 72 hours for otherwise nothing happens It has moreover nothing to do with the anaphylaxis problem for its effect is much more rapid and it is not related to any specific substance neither is it transmitted as Nicolle did when inoculating the blood of a prepared animal into a new animal Neither is it an allergy properly speaking when we refer to the sub-

stances employed for we can provoke a particular different sensitiveness with each of them

But what is beyond doubt is that this mechanism bears a resemblance to that of certain infectious diseases in man e g measles scarlet fever *smallpox etc*

In 1928 Schwartzman reports another fact After injection of a microbial filtered solution into a rabbit s gastric wall followed on the next day by an intravenous injection of the same product haemorrhage and necrosis of the local tissues set in at the point of the first puncture And this result is constant in any organ if it is prepared in the same manner[1]

Nevertheless this apparent experimental simplicity is variable in accordance with heredity climate food etc of the animals as is reported by Sulzberger at the Rockefeller Institute of New York at the clinic of the great immunologist Karl Landsteiner The following story is interesting in this connexion

About the year 1927 after this reaction of sensitivity to atoxic products had been verified by Jadassohn and others Sulzberger declares that Landsteiner was unable to obtain the same results with his guinea pigs despite all the resources of his marvellous laboratories The European *scientists thereupon offered to teach the Americans the exact* technique used in Breslau and Zurich, after making sure that the guinea pigs used were identical in size weight and colour Notwithstanding all their efforts however and great disappointment the experiments failed which made Landsteiner and his assistants doubtful of the truth about the experiments reported by the Europeans For almost 4 years after this dozens of experiments were made on guinea pigs which were sensitive in Europe but indifferent in the United States[1]

At long last the conclusion was arrived at that to produce the required sensitivity it is necessary to include the various factors mentioned above i e heredity food climate products utilized etc in a mixture of elements lacking any defined explanation and henceforth vaguely termed *idiosyncrasy* or in Bard s denomination *personal susceptibility*

The strange sensitizing substance which we call antigen or allergen provokes the appearance of a substance contrary to the antibody at the level of the live cell The conflict antigen antibody is frequently accompanied by a histamine discharge a kind of organic toxin which represents what we call in theory the allergic reaction Hence the application of anti histaminic medicines which by neutralizing the organic histamin subdue the reaction

In reality however the human diathesis goes beyond the researches of investigators and their theories however well imagined they may be So we sacrifice the existence of allergic individuals to these very anti-

histaminics and other allergics to any substance on a level with any and every organ—and this justifies us in affirming that allergy is an integral part of human pathology

New horizons are thus opened up to the physician in the truest sense of the expression The individual patient is an organic whole his reactions in the face of an infirmity may sometimes assume the aspect of a local affection, but they concern the entire organism which responds all according to the manifestations of the disease, with especial characteristics

It was on this basis that Selye the wellknown endocrinologist created his concept of *stress* a combination of aggressivity and reactions of defense with a corresponding state of general adaptation with its increase or decrease of the secretions in the three phases of the morbid process reaction of *alarm* period of *resistance* and state of *exhaustion* followed by death

Each patient is a case apart because each one is the bearer of his own personal sensitivity and allergy as we have seen is a reaction of the entire organism against anything—objects chemicals vapour light temperature smells dust fabrics—in short half of the entire milieu This reaction of the individual is completely independent of the product that may provoke it Its intensity and particular type are of so little consequence that my dear friend the late specialist Arnault Tzanck called this phenomenon *reactional pathology*

The conception of allergy has completely modified the notion existing until recently of a disease confined to an organ or group of organs We now consider the entire living field in which the reaction causes the whole organism beyond the visible clinical lesion to intervene after a period of time during which the sensitivity existed without our knowledge

There is the case for example of the surgeon (referred to by Leriche) who one day during an operation pricked his finger through a rubber glove Being an incident of no importance it was forgotten until the surgeon noticed that whenever he did any manual work the phalanx of the pricked finger would go hot and cold for some minutes per day Some months later he happened to hit it rather hard against some solid surface and noticed an intense redness followed the next day by an abscess with pus at the very point of the original puncture!

Another case is that of a woodman who during the war was shot in the arm The alterations of the injured nerves were conveniently treated and the man was able to resume his normal life without any trouble whatsoever But one day ten years later, while sawing a tree —his usual daily job—he suddenly felt a persistent pain precisely affecting the nerves formerly hit! For ten years this man had forgotten

the accident but his tissues his organism had remembered and re minded him!

There is also the very interesting story told recently by Louis Delmas in *La médicine totale* about the old alpinist who for seventy one years had moved about without any painful symptom fatigue or limping although he had a deformed knee that had been treated at the age of eight and which after all these years without any apparent cause has set up an enormous extremely painful haemarthrosis to remind him of the old alteration of the articular surfaces

How many similar cases have we doctors not seen passing through our consulting rooms? Do alterations in the nervous circuits complex cause the organism to react at a distance under a pathological influx of the moment?

Disease—as Tzanck again affirms—is a story that cannot be told by bits neither in space duration or evolution This axiomatic notion revolutionary in the serenity of Pasteurian medicine of the beginning of this century confirms the essence of the theories expressed by my dear regretted friend Auguste Lumiere theories which he expounded so modestly in his book La maladie cette grande inconnue

Having appreciated the allergic phenomena resulting from individual sensitivity one readily understands the reason for the influence of crenotherapy in the treatment of affections of this nature The anti allergic properties of mineral water act in a complex manner not only locally on the organ treated but also by favouring organic disintoxic ation modifying the predisposition either hereditary or acquired and favourable to the occurrence of allergic manifestations Without a truly specific action whether curative or experimental it is unquestionable that there is an advantage in the adjuvant application of crenotherapy for the resolution of the morbid factors whether general or local

For Doerr Jadassohn Diedey Berger Hansen and others affections are allergic only when the existence of an antigen antibody reaction can be proved But since this frequently eludes the best methods of investiga tion we have to consider the affections whose anamnesis and clinical observation show the characteristics of allergy and give way to the respective treatment Let us then classify them according to the ortho doxy of the processes

a) Purely allergic affections They manifest themselves normally by a sericeous exanthema or in the form of polyarthritic perturba tions myalgia oedema etc alimentary and medicinal allergies urticaria angioneurotic oedema vasomotor rhinitis hay fever bronchial asthma migraine Ménière s disease eczema neuroderma titis etc

b) Affections with an inflammatory allergic factor or an allergico

infectious one as glomerulonephritis endomyocarditis, polyarthritis tuberculosis etc

c) Affections in which the existence of an allergic factor can be recognized the pregnancy toxicoses sclerosis in plaques, gout gastritis gastro enteritis colitis neuritis etc

The allergens or antigens may be classified as follows

1) Exogenous allergens those which penetrate the organism from out side

2) Endogenous allergens elaborated by the organism itself or by bacteria existing in it (focal infections)

3) Allergens of invasion deposited by parasites on or into the organism

4) Physical factors cold heat light pressure etc

The exogenous allergens are subdivided thus

a) Allergens by inhalation pollen of plants dust various powders etc

b) Allergens by ingestion foods (milk eggs fish strawberries tomatoes artichokes etc) and medicines (bromides iodine salicy lates barbiturates sulphones compounds of thiouracil javel water parapheniIeudiamines alkaloids)

c) Allergens by contact Products of vegetable or animal origin that come into contact with the skin or the mucosa, e g horse hair silks nylons cosmetics rubber etc

d) Allergens by injection penicillin streptomycin the poison from the bee s sting of from spiders or bed bugs This group also includes the sera and the Rhesus factor

When prescribing a hydromineral treatment for an allergic patient it is necessary to obtain the best results to establish exactly the nature of the affection the constitutional ground to be modified and the correct application to be used It is ignorance of these factors that is nearly always responsible for the lack of success which both disheartens the patient and discredits the waters[1]

Another aspect to be borne in mind is that the water cures should never be applied during an acute period of allergic crises but only in the intervals In the former periods crenotherapy is usually badly tolerated with exacerbation of the syndrome because of the local and general reactivity normally provoked by the waters at the beginning of their being used

Various hypotheses have been put forward for the application of mineral waters to allergic affections Thus Billard in 1913 tested the anti anaphylactic effect of the bicarbonated chlorated carbogaseous and arsenical waters of Royat in France by sensitizing a laboratory animal with horse serum and treating it daily for three weeks with subcutaneous injections of water test After some time had passed he verified by a

new injection of serum the harmlessness of this injection as compared to another non desensitized test animal

The same results were also arrived at by Flurin and Armengaud with the sulphurous waters of Cauterets, by Perrin and Abel with the bicarbonated sulpho-calcic water of Vittel and by our countrymen Feliciano Guimaraes and Gouveia with the sulphocalcic waters of Curia However the latest investigations appear to confirm the hypo thesis that crenotherapy effects a modification in the humoral and neuro endocrinous system and does not act directly on the allergic *sensitizing element which explains the identical results obtained in* clinical practice from waters of different mineral composition and concentration Thus *sulphurous waters* find a wide application in certain forms of allergic disease particularly in bronchial asthma in rheuma tism and in certain dermatoses thanks to their antiphlogistic action and their trophic and protective effect on the mucous membrane as well as being a reconstituent equilibrator of the endocrine neuro vege tative system and of the metabolism of carbohydrates in addition to the specific role which they perform in the activity of the hepatic cell and the consequent modification of the constitutional system

Of this nature are our waters of Vizela Taipas Caldas da Saude Canavezas Moledo do Aregos S George Entreos Rios S Pedro do Sul Felgueira Manteigas the S Paulo baths at Lisbon among the sulphurous sodium waters and Caldas da Rainha among the sulphurous calcic waters They are used by way of cutaneous immersion baths by way of direct inhalations and from the patients milieu through the respiratory organs by ingestion in the form of drinks in genito urinary diseases by irrigation and by subaquatic enteroclysis

The *chlorated sodium waters* are administered in various forms e g gastrically on an empty stomach when they are indicated in allergic cases connected with gastro entero hepatic dysfunctions They also act on the organic metabolism by their general disintoxicant action by means of baths inhalations pulverizations etc This group includes the waters of Cucos Estoril Termas Salgades Batalha St Martha Castelo de Vide etc

The alkaline waters of the group called *bicarbonated alkaline earthy bicarbonated sulpho alkaline and bicarbonated earthy sulpho alkaline* are administered by baths *inhalations irrigations etc According to* several authors they act on allergic manifestations connected with entero hepatic disorders and on those of a gouty origin In view of their calcigerous content their efficacy is notable as diuretic antiphlo gistic remineralizing and sympaticothropic agents Of this group the waters of Pedras Salgadas Vidago and Salus Chaves Monção and Monchique are predominantly sodium bicarbonated those of Melgaço

and Moura are calcium bicarbonated those of Curia and Monte Real sulpho calcic The chlorated bicarbonated carbo gaseous waters are being used with magnificent results in the treatment of bronchial asthma in inhalations They act on the nasal mucus and as an anti congestive on the bronchial tubes This group includes especially the famous French waters of Mont Dore and Royat

The radio active waters have a beneficent action on allergies of a neuro-vegetative and hormonal origin as modifiers of the organic diathesis This group includes the waters of Abrunhosa Alcafache S Gemil Urgeiriça Luso and Curia whose radioactivity generally exceeds the 2 millimicrocuries per litre i e the rate demanded by Violle in his Actualites d hydrologie et climatologie médicales for a mineral water to be called radio active

The hydromineral waters mentioned above, which are effective in modifying the organic diathesis are much favoured in our country the Gerez ones are especially worth mention being hyposaline they contain a very high percentage of sodium fluoride which makes them unrivalled in their kind all over Europe

Apart from the hydromineral factor proper one should also bear in mind the need for a satisfactory climate and for pure air, free from allergizing factors

Summarizing we may affirm that

1) Crenotherapy by its disintoxicant action and as a modifier of the humoral and neuro vegetative system is a treatment of great value as a complement to a rational anti allergic therapy

2) It should never be employed during a period of acute allergic crisis

3) To ensure its favourable result in allergic patients there should be perfect co operation and synchronization between the allergist and the hydrologist so that the nature of the affection can be correctly diagnosed the constitutional system to be modified can be determined and the right application decided upon

4) Portugal by virtue of its hydro mineral wealth can rival any country in this respect there only remains the necessity of creating —as I have been advocating for a long time—Centres of research and treat ment of asthma and allergic diseases where specialists may work and improve their technique of arriving at an exact diagnosis and the right application of remedies

Literature

DALMAS LOUIS *La médicine totale* Paris 1954

GUIMARÃES FELICIANO GUIMARÃES J LOBATO *Hidrologia médica Aguas minerais de Portugal* 1954

LUMIÈRE AUGUSTE *La maladie cette grande inconnue* Paris 1949

MESSINI MARIANO *Trattate de idroclimatologia clinica* Bologna 1950

MORA MÁRIO DAMAS *A importancia social das doencas alergicas* Lisboa 1950
— The formation of investigation centres and treatment of allergic diseases *Acta Allergologica* Vol VI Fasc I 1953
PRODUITS CIBA *Annales* 1953
SANGIORGI PIERO *Principi di Allergia Clinica* Milano 1950
TZANCK ARNAULT *La conscience créatrice* Paris 1944
URBACH E GOTTLIEB PH M *Allergy* New York 1949
VALLERY RADOT PASTEUR *L Allergie* Paris 1951

LUG WORM (ARENICOLA) SENSITIVITY

by

A W FRANKLAND

The lug worm or lob worm (*Arenicola marina*) is a common worm found living in the sand between tide marks on the sea shore It is often used in sea fishing as a bait The following is an account of a patient who developed a sensitivity to lug worm

The patient was a man of 52 years, who had fished with lug worms since he was a boy His occupation was a porter in London but twice a week he went down to the coast to fish on his half day holiday In 1954 he noticed that when he went to fish at Hastings the same evening he developed asthma He was free at all other times One day he decided to fish at a new place and he chose Dover He was pleased to find that he was free of asthma after fishing there He then remembered that he had only used mackeral fish heads at Dover as bait He tried this bait at Hastings but caught no fish and also for the first time after fishing there had no asthma The next time using lug worms at Hastings he again developed asthma He also found that if he went to Dover and fished with lug worms he developed asthma there too

He was sent to me as a patient who stated that lug worms caused asthma and so far as he knew nothing else Further questioning brought to light the fact that when threading the worm on the fish hook he had recently noticed an irritation of his fingers An extract of lug worms was prepared A hundred known allergic patients were tested with the extract Nine of them gave a doubtful (+) positive response The patient gave a definite (++) positive response All other skin tests to common allergens were negative He has been advised to give up using lug worms as bait

The interest in this sensitivity which has not been described previously is more in the possible manner of absorption of the sensitizing antigen The worms were kept in a tin The only contact with the very moist worms was when he threaded the fish hooks Apparently it was during this time that the lug worm was in some way absorbed This produced a local urticaria of the fingers and asthma

STATUS ASTHMATICUS IN THE PATIENT S HOME*

by

M J GUTMANN

May I ask you to depart in your minds for a while from your well equipped and smoothly functioning clinic or hospital where a mere glance at your assistant will rouse the latter to action and where your accompanying nurse can read your wishes in your eyes and executes them implicitly Imagine yourself in a private home of rather modest standing surrounded by the more or less excited members of the patient s family The treating physician who had asked you to come over is absent and all you know from him is the diagnosis of status asthmaticus which he mentioned on the phone

In *whatever condition the patient be he is not capable to furnish* any information and you must fall back entirely on your own faculties of perception on your discerning eye your keen ear your tapping finger sometimes even your sharp nose and eventually on your own experiences

Remember that of all the methods appropriate in hospital but few are applicable here Whereas every available assistant widens the scope of your therapeutic possibilities while you are all on your own you can only do *one* thing at a time in those serious situations that we are going to discuss the sequence of the steps you are going to undertake may prove of the greatest sometimes even of decisive significance—there fore—first things first You will be wise if you ask all but one of those present to leave the room and to prepare some boiling hot water at once—for reasons which will presently become apparent Such request will moreover reconcile them for having been ordered out as they can now busy themselves with something for the patient s benefit

Situation I Patient is unconscious

The condition is serious and seems endangering the patient s life—but there is hope—so at least you should tell the family

The patient is reported to have been unconscious for some short time only He is cold and clammy, in deep cyanosis his pulse is just palpable and rapid respiration is slowed down and failing and you think that this is the end One glance will tell you that during the past hours the patient has received numerous adrenalin injections perhaps he even administered them himself judging from the syringe and the empty

From Consultant in Allergy a collection of practical experience

ampoules that are scattered around and from the red and swollen spots on his tighs They are the preferred place for self administered injections unskilfully executed with part of the adrenalin remaining in the skin and simulating adrenalin resistance a subject we shall return to presently You might also find inhalation apparatus for adrenalin or aleudrin (isuprel) or may be one of those dangerous electric aerosol sprayers which can be operated any time without effort and without control and which are therefore frequently overapplied

At this point you must not waste time It is true, we know that such states of unconsciousness of anoxemia will sometimes pass spontane ously within a few seconds but if they persist for more than one minute swift action is imperative Do not let yourself be deceived into despair of futility nor should you heap indiscriminately medicines thinking that while matters are too far gone to be upset any more you can just only win if anything

Three things demand your immediate attention respiration heat and fluid supply Remove the pillows from beneath the patient s head until you have him flat on his back and start straight away with the Res piration by pressure on the diaphragma a procedure with which you should technically be well familiarized Clasping the patient s abdomen below the ribs between both your outstretched hands you press the intestine upwards thus driving air out of the rigid thorax and repeat *this movement rhythmically for some time As soon as the first deep* breath surges up at least quo ad vitam the situation has been largely brought under control

Once respiration is established you can rub in the above mentioned Adrenalin depots as we may call them now thus introducing appre ciable dosis of adrenalin into the blood stream Let us remember that until now the patient could not be left alone so we had no opportunity to prepare an injection even before doing so we better clean his throat with a mounted swab such as should always be ready in our emergency outfit

Meanwhile we may have managed with the family helping to place hot water bottles around the patient and to feed him some hot tea with glucose (that we brought along) At this stage it depends on circumstances and subject to ones experience whether to try injecting intravenously aminophyllin or small fractionated doses of subcutaneous adrenalin I have repeatedly witnessed in such conditions a marked motor unrest in patients just coming round out of the unconscious state It was then impossible to get in an intravenous injection whereas a subcutaneous one met with no difficulty adhering to the principle of small repeated doses of 0 1—0 2—0 3 cc every other while until the attack is broken (though I myself have at no time even remotely approached such doses

as E A Brown (Boston) recently described a case of an asthmatic attack after aspirin where it took 6 hours and almost 40 cc epinephrine to pull the patient out of this attack (each minute 0 1 cc subcutan) It is imperative that the physician not leave the patient before he is safely out of the attack in case the doctor is urgently bound to leave he should have a colleague take over

What should on no account be given in situations such as these are big single doses of epinephrine never intravenous nor ever intracardial no morphine or the like and no antihistamines emetics be given no sooner that the patient has been restored to full consciousness

Situation II The asthmatic with orthopnoea

The patient is conscious but unable to breath except in the upright posture deeply exhausted and gasping for air cyanotic The family report that until a few minutes ago he was breathing so noisy that he could be heard in all rooms that he had quietened down now and you can see they take this as a sign of improvement

One glance at the patient will suffice to inform you that this is a false interpretation and a dangerous one as pointed out by Leon Unger s statement (*J A M A* 150 562 Oct 11 1952) It is better to have a noisy patient than one who is quiet and unable to expectorate Here is your first task to make the patient noisy again The patient is likely to lean over a table or chair he is bathed in sweat and highly anxious You will hardly have a chance there to apply diaphragmatic respiration nor will you be able to get in an i v injection the patient being so rigidly persistent his peculiar posture that even moving his hand for immersion into hot water will prove impracticable This latter procedure by the way is often surprisingly successful and can be applied to the feet as well possibly with the aid of the family

If intravenous injection is possible I prefer aminophyllin alone or composite with 1 gr sodium iodide slowly introduced Sometime addi tion of papaverin is badly tolerated whereas morphine may even cause fatal calamity A small dose of dolestine (pethidine) of 25 – 50 mgm will relieve many patients provided tolerance for this drug has been previously asserted we invariable give it in combination with epine phrine even in cases which are reputably resistant to epinephrine Similiarly the antihistaminics while aggravating bronchial asthma by just their dessicating action which we try to avoid yet enhance the efficacy of epinephrine This seems to be due to the antihistaminics *neutralizing the histamine outpour which tends to inhibit the adrenalin* thus leaving the latter free to act

Excellent results are often achieved by inhalating of isuprel (iso drenal) through a simple apparatus with a mask Whereas the mask is

essential electric operation of the apparatus is not and the simple device can be conveniently added to the rest of the emergency equipment taken along for action against asthma The bronchi often respond to these means when they do not longer react to adrenaline

It is amazing to behold the relief the patient experiences after the first expectoration as he can recline again from his standing or sitting position In order to replace the fluids that the organism has lost and replenish liver glycogen from the liberal administration of adrenalin warm and sweet drinks are indicated at the earliest possible time

For the prevention of immediate relapse ACTH gel is at present the drug of choice and should be given whenever it is not contra indicated for some other reason At times fever therapy will secure the desired end Obviously certain circumstances must be duly considered in treating the asthmatic state such as infancy gravidity hyperthyroidism high blood pressure etc

In the somewhat inopportune conditions prevailing in the patients home you will do well to choose the direct approach Try anything to make your patient caugh up and besides supplying warmth in every possible manner hold on to iodine aminophylline and epinephrine

Situation III The asthmatic physician in the asthmatic state

Theoretically at least treatment of the asthmatic physician should be guided by much the same principles as that of any other patient Actually however deviations occur which may easily prove detrimental to the colleague s wellfare My own results at treating colleagues are not markedly worse then those attained with ordinary patients for two reasons Nowadays laymen are fairly well acquainted with the nature of their afflictions and in a general way the means by which they can be cured they are lacking however judgement as to the different possibilities presented by each particular case Physicians usually fail similarly when their own condition as sufferers has to be evaluated and they tend either to exaggerate or else to underestimate their case The greatest danger is to be found in overdosage of drugs and polypragmasy particularly in status asthmaticus

Suppose you are called to look after an elderly colleague of say 50—60 years of age Be sure to find him at the electric inhalator containing a new and even more concentrated inhalant than those in general use hitherto Here again empty ampoules bear witness to quantities of adrenalin having been injected already as well as intramuscular aminophyllin Your patient gasps for air is restless blue red in the face and you can see the veins on his forehead pulsating wildly He craves for more injections or whatever remedy to grant him relief and relaxation To watch him suffer is quite a strain on your own nerves You remember

he had a coronary occlusion some years ago and you feel a strong urge to let him have some morphine or something of the kind Now do not let yourself in on this Temptation for polypragmasy is strongest on such occasions If on the other hand you rapidly survey the situation critically it will occur to you how pale he was after that last adrenalin injection how even now he still trembles that pressure is high in the hardened tortuous blood vessels and that every new injection can only aggrevate his condition At this point a shot of luminal will go far way in putting your patient at ease if you can manage to perform a venesection with some assistant s help a blood letting of 300 cc will be most beneficial As soon as everything is more tranquil and you have the patient reclining you are out of the worst and can then institute further therapy either with fractionated epinephrine injections or anything else All this will take some time and you will find the restive and impatient features of your colleague make way to a more complacent expression You may put up placidly with his reproaches that you should have acted more rapidly had you given in to your first mood under the circumstances you would may have done a lot of harm

One colleague who was very cross with me for refusing him morphine at a critical stage called in another colleague a few weeks later who gave him what he demanded so emphatically He may well have paid for this with his life when he expired some hours afterwards No effort must be saved to impress the patient with the importance of preventing subsequent attacks Unfortunately your endeavours of systematic therapy are often undone by the application of all sorts of new and unwarranted means and methods

Where their own health is concerned physicians lack discrimination as else they should know that most of the newly recommended methods disappear from the literature within a few years and that new improved drugs are not granted permission to advertise in the medical press Each one of us knows plenty of such instances

The proper executed therapeutic measures with colleagues should be carefully observed since otherwise they are liable to turn harmful agents through wilful correction

Luckily—and in order that justice be duly pronounced—there are many suffering colleagues whose co operation greatly alleviates our work and enables us to score successes which can not be secured with the average patient

PROBLEMS OF INVESTIGATION IN ASTHMA

A comparison between the results of experimental studies on animals and clinical studies to gain a better insight into the pathogenesis and clinical picture of bronchial asthma

by

GOTTFRIED HOLLER

In reading this paper I intend to briefly review what I have previously written on the subject as well as a detailed study now in the press to be published in the Acta Neurovegetativa This study is mainly based on the results of experimental investigations by J Kracht and his associates as well as those of earlier studies by others on The control of the secretion of thyrotrophic and adrenocorticotrophic hormone with special reference to thyrotoxicosis of emotional origin the results having been compared with those of personal studies on cases of human bronchial asthma The working hypothesis based on these data is chiefly intended to afford a better insight into the pathogenesis of bronchial asthma in which the disturbed correlation between the endocrine glands probably plays the most important part

To begin with the fact cannot be overlooked that allergic diseases in civilized countries all over the world are increasing to such an extent that to day they have frequently come to be endemic Of these diseases bronchial asthma being the most distressing and troublesome of these forms of illness which sooner or later results in incapacity for work and invalidism in the great majority of cases deserves special attention By my calculation there are about 15 000 patients with asthma in Austria

I need hardly draw attention to the fact that an infinite number of living and inanimate substances having the character of allergens are constantly invading our organism from the outside world and that an equal number of allergens may develop endogenously from a wide variety of lesions to our own cells and tissues which then produce auto-antibodies giving rise to conditions of allergic and hyperergic reactivity so that they come to be the most important factors in the pathogenesis of various forms of disease and especially in bronchial asthma

A case in point is drug allergy about the most common cause of which is the excessive use of penicillin and in which all kinds of conditions of allergic and hyperergic reactivity ranging from the mildest to the most severe forms (including anaphylactic shock, periarteritis nodosa allergic arteritis thrombo-angitis dermatitis exfoliativa bronchial asthma and other allergic diseases classified to-day as collagen

diseases in view of their common pathogenesis) are seen to occur My head nurse who until that time had never shown symptoms of allergy and whose familial history was negative was often present in rooms where penicillin was being inhaled as an aerosol Being obviously predisposed in this regard she was sensitized to the fungus derivative which I have found to be a highly effective allergenic extract especially when used in inhalation therapy Initially this resulted in allergic bronchitis which my assistant believed to be due to infection wrongly deciding to treat this condition with inhalation of penicillin aerosols Even the first inhalation of 100 000 U of penicillin was followed by the appearance of typical bronchial asthma This was subsequently associated with perioral dermatitis (involving those areas of the skin which had been covered by the breathing mask) stomatitis and glossitis An attempt at desensitization by intradermal injection of a very small dose of penicillin (1000 U) resulted in extremely severe anaphylactic shock The patient s life was saved but she continued to be highly sensitive to penicillin In addition the clinical picture of this patient was characterized by the fact that for years after the event the 24 hours urinary elimination of 17 ketosteroids failed to exceed the low level of approximately 6 mgm (the physiological level in women is about 10 mgm) This was interpreted by me as evidence of hypofunction of the adrenals, another symptom being the eosinophilia of the blood In addition, dysproteinaemia an increase in the number of γ globulins in the serum as revealed by electrophoresis and an increased erythrocyte sedimentation rate furnished evidence of hyperplasia of the reticulo-endothelial system concerned in metabolism

The case of my head nurse has its counterpart in the guinea pig sensitized by injections of chick albumen which always immediately has an attack of asthma and dies from anaphylactic shock in an atmosphere charged with aerosols of chick albumen When sufficient doses of cortisone or ACTH are injected into this animal which is susceptible to anaphylaxis after it has been sensitized with chick albumen it will always survive the chick albumen aerosol Likewise administration of cortisone and (with certain exceptions to be discussed later) also that of ACTH will result in the disappearance of any form of bronchial asthma (even the most severe type of status asthmaticus)

With my associates, I have studied the data reported in the literature and I was able to determine a diminished urinary elimination of 17 ketosteroids in the resting state in about one third of my patients with asthma (the decrease always being most marked following severe attacks) The Thorn test revealed the deficiency of the pituitary adrenocortical system (or impaired function of the adrenal cortex) in the other two-thirds In my opinion it is this hypofunction of the adrenal cortex

(or of the entire diencephalopituitary adrenocortical system) which frequently is hereditary that predisposes the patient to bronchial asthma One of the various functions of this general defence mechanism is to keep the production of antibodies and the attachment of antibodies to cells within suitable physiological limits by cortisone (gluco corticoid) the hormone secreted by the normally functioning adrenal cortex so that undesirable antigen antibody reactions will be prevented When this mechanism is unable to do so as too little cortisone is available the invasion of the body by allergens causing excessive production of antibodies and attachment of antibodies to cells (sensitization) will inevitably result in a condition of allergic and hypergic reactivity When the same allergen again enters the body which chiefly occurs via the lung in bronchial asthma this results in antigen antibody reactions in the bronchial mucosa An allergic inflammatory reaction marked by tumefaction and increased secretion from the mucosa sets in Finally the stricture of the bronchi is increased by a reflex spasm of the bronchial muscles (attack of asthma)

As stated previously this condition may be controlled by treatment with cortisone (substitution therapy bronchial asthma as a disease of adaptation in the sense of Selye) whereas it can only be controlled by ACTH when sufficient cortisone is still available in the adrenals its secretion being induced by this artificial stress caused by ACTH

Even the earlier literature published about twenty years ago refers to the fact that a number of disturbances of endocrine correlation may be detected in bronchial asthma Hyperthyroidism being one of the most important of these disorders I shall briefly review this condition The great majority of my patients with asthma showed increased basal metabolism (the increase being very marked as much as over 80 per cent in some cases) Surprisingly the respiratory curve showed sympathicotropic characteristics (naturally in the intervals between attacks and when certain measures were taken to control the amount of supplemental air in the lungs) There are several facts but particularly the increased specific dynamic action of foods (especially meat) observed in my cases which provide evidence suggesting that the increased oxidation in this case is primarily induced by the metabolism centre in the diencephalon which increase subsequently results in impairment of the function of certain endocrine glands Obviously the gland most likely to be involved is the thyroid it is the chief regulator of metabolism and impairment of its function is most likely to give rise to a marked deviation of the respiratory curve The basal metabolic rate in acute attacks of asthma status asthmaticus and spastic bronchitis does not afford any indication as to the intensity of the processes of oxidation Therefore basal metabolism was only determined when vital

capacity had attained a level of at least 2500 in women and 3000 in men

The study of cases in human subjects has shown that exophthalmic goitre is characterized by hypofunction of the adrenal cortex to the point of atrophy and from experimental studies on animals it is known that an increased secretion of thyrotropin and thyroxine (implying predominance of the diencephalic pituitary thyroid system over the diencephalic pituitary adrenocortical system) such as may e g be induced by emotional impulses (emotional hyperthryroidism in wild rabbits) results in more or less marked inhibition of the secretion of corticotrophin (ACTH) and cortisone as well as retrograde changes of the adrenal cortex In my opinion this disturbance of the synergy between the two mechanisms the diencephalic pituitary thyroid system which responds to specific stress and the diencephalic pituitary adrenocortical system which responds to a wide variety of impulses occurs in bronchial asthma to the detriment of the latter system The primary cause of this disturbance may be either hypofunction of the adrenal cortex or hyperfunction of the thyroid So far it has been impossible to sharply differentiate these two types of pathogenesis of bronchial asthma into a thyrotoxic and an asthenic form I shall merely point out the fact that treatment in cases of bronchial asthma showing exceedingly high basal metabolic rates (over 50 per cent will only be successful when very large doses of cortisone and ACTH are administered In addition it is of importance to know that administration of antithyroid drugs which suppress the production of thyroxine in the thyroid which results in increased secretion of thyrotropin from the anterior pituitary and in turn disturbs the balance to the detriment of the ACTH will aggravate the asthma On the other hand iodine which has always been useful in the treatment of bronchial asthma will restore the normal function of the thyroid This inhibits the secretion of thyrotropin some degree of synergy between the two hormones is achieved and the patient will feel relieved

This was the only thing I wished to say regarding my studies on the role of the endocrine glands controlled by the autonomic nervous system in bronchial asthma The nervous portion shows the known symptoms of dystonia of the autonomic nervous system (impairment of nervous control) resulting in vagotonia in the region of the bronchial tree Nervous and humoral processes interact the disturbed correlation between the endocrine glands causes abnormal reactivity of the autonomic nervous system extending from the centre as far as the periphery and this in turn further impairs the hormonal and therefore the humoral metabolic processes (*the physico chemistry of our organism*) This condition may be corrected to some extent by treatment with neurotropic drugs (sympathomimetic and vagolytic agents) and also as has

been shown by experience by psychotherapy so that a condition ranging from more or less transient relief to suppression of the asthma may be obtained This is not the only result however for this period is also marked by a decrease of the number of changes in intermediate metabolism a typical feature of severe bronchial asthma When used correctly neurotropic drugs and methods accordingly show favourable effects identical to those obtainable by cortisone and ACTH, as stated previously although in this case the effects will be more persistent and more marked There is no objection to combining the two methods with a view to obtaining the best possible results In my experience administration of neurotropic drugs will be even more effective in bronchial asthma when it is combined with substitution therapy consisting in administration of cortisone

The antigen antibody reactions (chemical transformations) occurring in these cases of impaired metabolism are not only dependent upon the condition of the endocrine glands but are also controlled by the autonomic nervous system When the mesencephalon of an animal susceptible to anaphylaxis is blocked (e g by cutting the cervical spinal cord or by deep anaesthesia) the classical method of sensitization by injections of chick albumen will fail When chick albumen is injected into an animal already sensitized this will result in fatal anaphylactic shock To prevent this the peripheral portion of the autonomic nervous system must be paralyzed This experiment shows that once it has started an allergic mechanism cannot be arrested by the autonomic nervous centre in the diencephalon and that antigen antibody reactions are in the last resort induced by the nerve endings of the autonomic nervous system its intramural syncytium

Hibernation (anaesthesia or administration of morphine being less reliable) may be used to obtain the transient disappearance of the condition of allergic and hyperergic reactivity in cases of asthma Apoplexy put a definite end to the respiratory disturbance of a woman who had been affected with bronchial asthma for a period lasting several decades On the other hand the study of the literature shows that as I have observed myself in some cases head injuries (concussion of the brain) and cerebral lesions due to infection (following encephalitis) may be followed by the appearance of bronchial asthma The subjects involved are undoubtedly predisposed individuals (deficiency of the pituitary adrenocortical system) in whom an impulse arising from the nervous portion of the autonomic nervous system increases the hypofunction of the adrenal cortex which has been obscured up to that point and converts it into a clinical picture with the assistance of a temporary allergic reaction I am bearing in mind the fact that these cases are initially characterized by the appearance of a situational

thyrotoxicosis (Selye) corresponding with the emotional thyrotoxicosis of the wild rabbit so that the adrenal insufficiency is primarily induced or increased by a specific stress acting on the thyroid The above suggests that this type of disease is a thyrotoxic form of bronchial asthma The increased basal metabolism observed in 3 personal cases provides evidence supporting the theory of a situational organic disease predisposing the patient to an allergic reaction (bronchial asthma) by impairment of the pituitary adrenocortical system Hereditary factors were probably involved in only one woman whose mother was also affected with asthma

The clinical picture of bronchial asthma (as a collagen disease) includes symptoms of hyperplasia of the reticulo-endothelial system concerned in metabolism such as eosinophilia of the blood (demonstrable only in the bone marrow in some cases) an increase of the number of plasma cells in the blood or bone marrow removed by sternal puncture dysproteinaemia an increase in the number of γ globulins in the serum an increased erythrocyte sedimentation rate etc This hyperplasia of the reticulo-endothelial tissue plays a part in the pathogenesis for antibodies are mainly produced in the cells of the reticulo endothelial tissue and not the circulating antibodies but those attached to the cells are active Therefore the most rational method would be to reduce the fixation of antibodies to cells by saturating the reticulo endothelial tissue with stored substances and disturbing it This view is supported to some extent by the result obtained in treatment with nitrogen mustard which reduced the severity of the clinical picture in some cases of bronchial asthma Once again the results of experimental studies on animals afford a better insight into the conditions prevailing in these cases My associates Hammerl and Millesi injected thorotrast into guinea pigs sensitized with chick albumen Subsequently re injection or inhalation of a chick albumen aerosol failed to induce anaphylaxis in any of the animals to whom the radioactive substance had been administered The same result was obtainable with radioactive gold It is intended to try and treat patients with asthma with a radioactive substance having a small half life

In cases of soil dust asthma the form of asthma with which in my experience the greater part of the patients in Austria is affected it is very useful especially in the case of children to transfer the patients to places situated at an altitude of over 1500 m above sea level where favourable climatic and weather conditions prevail as soil allergens are absent in these areas A stay at these altitudes continued over several months or years will result in the disappearance of the disease In view of the large number of patients with asthma it is a matter for the public health services to take the necessary measures and found estab

lishments for a large number of individuals Excellent results have been obtained in the Alpine Children s Sanatorium Neuegg near Obladis (in the west of North Tyrol) in Austria Adults who fail to find relief in the very modern spas in Gleichenberg Ischl and Bad Hall as they encounter soil allergens to which they are susceptible I send to the places Zerfauss and Hochzerfauss (in the west of North Tyrol) to the Gorlitze (in Carinthia) St Jakob in Deffreggental (Red Cross establishment) etc which are free from allergens and have a favourable climate

Literature

HOLLER G *Acta neurovegetativa Vol I* 1954 p 1—2 *Acta neurovegetativa 13* 1956 p 2—3

TREATMENT OF BRONCHIAL ASTHMA

by

JULIO A MORETTI

Methods of treatment may be divided into methods used to control attacks preventive and curative measures used to prevent attacks in the future the elimination of specific agents as well as predisposing or contributing causes methods which modify allergic reactions symptomatic medical treatment

HOW TO CONTROL ATTACKS

Administration of small doses of a 1 per 1000 solution of adrenalin not exceeding 0 05 ml per injection An effective method is to give doses of 0 02 ml every 3—5 minutes leaving the needle in place When it is advisable to prolong the action of the adrenalin a deep subcutaneous injection of one half—1 ml of an oily solution is given One should be able to detect the first symptoms of intolerance to the drug such as chills, tachycardia palpitations etc so that it may be withdrawn and replaced by other drugs When 1 per cent adrenalin is administered by aerosol the atomizer should be placed between the lips with the mouth half open and the patient made to inhale deeply as each jet of spray is thrown Atomization is obtained by powdered norisodrine or theophylline The secretions are fluidified by sprays of 5 per cent ammonium chloride Sublingual administration of 10—15 drops of a 1 per 1000 solution of adrenalin is useful

Adrenalin should never be injected too close to the surface as its ischaemic action may give rise to scabs Particular care should be observed in the treatment of hypertensive subjects and the blood pressure should be determined after each injection

Treatment with suppositories or injections of aminophyllin results in mental stimulation has an action on the cardiovascular system and increases the secretion of urine The aqueous solution used in intravenous injections varies from 20—40 per cent no more than 0 40 g should be given per dose twice or thrice daily Intramuscular administration is painful Theophyllin or aminophyllin may be used alone or combined with ephedrin phenobarbital or antihistaminics

Treatment with ephedrine consists in the administration of 0 05 g thrice daily In view of its congestive action particular care should be taken in treating elderly subjects with hypertrophy of the prostate as it may cause retention of urine Dysmenorrhoea and nervous dusturbances may also be observed

Magnesium sulphate has a marked bronchodilative effect 10 ml of a 10 per cent solution are injected intravenously Also 4 ml of a 50 per cent solution may be injected intramuscularly

Subcutaneous injections of ½—1 ml of a 1 per 1000 solution of atro pine produce paralysis of the vagal nerve endings The same can be said of belladonna

Despite their antispasmodic effects atropine and other derivatives are characterized by the fact that they dry up the bronchial secretions so that expectoration already difficult is obstructed to an even further extent

Antihistaminics are not very effective in asthma We believe them to be effective in cases of allergic asthma without complications Antihista minics are not only useful from the therapeutic but also from the diagnostic point of view as we can be sure that the asthma is due to allergy when they are effective

Coramine 5 ml injected intravenously

Novocaine or *Procaine* 1 per cent solution injected intravenously

Ephedrin and *Phenobarbital*

50 per cent *Glucose solution Injected intravenously*

Bronchial aspiration with lavage of the bronchial tree by a physio logic saline solution

CO_2 is used to eliminate accumulated matter in solutions of 5—10 per cent with 90—95 per cent of O It should be used *with care* in cases of heart failure It *must not* be used in pulmonary haemorrhages severe emphysema acute pleurisy and hypotension

Insulin shock therapy stimulates the production of adrenaline by the adrenals

Pneumoperitoneum elevates the diaphragm In addition it has a stimulating effect on the nervous system and reflexes (300—900 ml of O)

Lumbar puncture a few ml of cerebrospinal fluid are removed the action of this procedure is obscure

Surgical sympathetic block

Instillations of iodine (lipiodol)

Potassium iodide increases the secretion of urine and causes elimina tion of sodium retention of which aggravates the condition of patients with asthma The ingestion of chlorides is diminished (?)

HOW TO TREAT STATUS ASTHMATICUS

When the above methods of treatment have failed the following drugs are employed 1 ml of ether per kg body weight with an equal quantity of oil administered rectally by a thin tube To induce sleep it should be administered within 20 minutes and to induce semi anaesthesia within 1—2 hours The dose may be repeated every 6—8 hours

To avoid environmental factors and air borne allergens the patient should be hospitalized in an atmosphere free of allergens

Oxygen alone or oxygen with helium in a proportion of 80 20

It is advisable to place the patient on a water diet for some time to eliminate food allergens Laxatives per rectum should be given to remove food and other allergens

Intravenous injections of a 1 per 1000 physiologic saline or isotonic glucose solution of adrenalin should be given

Cases of status asthmaticus associated with hypotension tachycardia and precordial pain should be treated with xanthine derivatives 0 50 g of theobromine thrice daily aminophylline caffeine especially in jections

Treatment with morphine is contraindicated as it may cause death by inhibition of the cough reflex and by reducing the excitability of the respiration centre

Intravenous injections of 100 ml of a 50 per cent glucose solution with *0 5 ml of a 1 per 1000 solution of adrenaline*

One litre of an isotonic glucose or physiologic saline solution care fully mixed with *1–2 ml of a 1 per 1000 solution of adrenalin* the injection should never be completed within less than one hour

Of the 1 per 1000 solution of adrenaline 1–2 ml diluted 10 times may be injected intravenously and very slowly the injections being dis continued on the appearance of pallor tremors perspiration headache or dyspnoea

Bronchoscopic aspiration is indicated in cases in which expectoration is difficult An average dose of 20 mg of ACTH is injected intramuscularly every 6 hours for 48 hours when the patient shows an improvement after this *time the doses are progressively decreased A total dose of* 400–500 mg may be administered Smaller doses may be injected intravenously

The initial dose of cortisone should be 200 mg daily preferably ad ministered orally the dose being decreased subsequently while obser ving the course of the disease The patient should be placed on a suitable diet An isotonic glucose solution should be used for dehydration 1000–3000 ml being administered in 24 hours

The sodium content of the body decreases in the event of vomiting marked *sweating or profuse* expectoration treatment with physiologic saline solution is indicated in these cases and when the blood volume continues to decrease plasma should be administered to prevent hypo proteinaemia Especial treatment is indicated when dehydration is accompanied by the excessive use of sedatives as otherwise the patient may die

Hypopotassaemia results from administration of excessive quantities of

glucose solution and epinephrine The normal K content of the blood varies from 16 to 22 mgm When the concentration is 4 mgm respiration is weak when it is 3 mgm breathing is laboured and when it has diminished to 2 5 mgm dysphagia and paralysis associated with characteristic changes in the electrocardiogram (prolonged P—R interval lowering of the S—T segments and faint T wave) are observed

Treatment consists in administration of 3 g of potassium chloride or potassium citrate every 3 hours 6 doses being given per 24 hours The diet should contain large quantities of potassium chicken oats and orange juice

Acidosis caused by vomiting or malnutrition is treated with sodium lactate plasma or physiologic saline solutions

Alkalosis is hardly ever observed in attacks of asthma It is due to excessive expectoration This condition is treated with administration of 1 g of sodium biphosphate every 3 hours or glucose given orally or intravenous injections of dextrose

Hypoproteinaemia gives rise to the following symptoms loss of weight dryness of the skin and tongue subcutaneous oedema It is treated with plasma and injections of amino acids combined with glucose and plasma

Supervision of the general condition and administration of vitamins is essential

The inhalants causing the attack should be eliminated

Abstraction of 400—500 ml of blood is useful in some cases of asthma with cardiac complications or hypertension

PREVENTIVE TREATMENT

When one or both parents are allergic the children should be closely observed with a view to detecting possible symptoms of allergy such as cyclic vomiting vomiting and diarrhoea following the ingestion of certain foods urticaria and infantile eczema

During pregnancy women should be warned not to eat excessive quantities of food or foods known to be highly allergenic as sensitization of the foetus has been shown to occur via the placenta

Marriages of allergic individuals are not advisable and if they marry they should avoid having children as heredity has been shown to play a decisive part in allergic conditions

It is essential to start treatment as early as possible as soon as the first symptoms of asthmatic crisis have been detected The patients should be shown how to give themselves injections of adrenaline as waiting for the physician may frequently convert an ordinary asthma attack into a status asthmaticus

Patients who have given themselves many injections of adrenalin or taken ephedrin should be placed on a *high carbohydrate diet* or given

glucose solutions as these drugs result in the decrease or disappearance of the hepatic glycogen This treatment will protect the liver To day it is known that the serum proteins (and therefore the globulin to which the antibodies adhere) are produced by the liver Many authors believe that antibodies are produced only by the hepatic parenchym

General hygiene rest no violent exercise or massage in severe cases No copious meals especially no heavy suppers

Fried food fats underdone foods should be avoided No spices

Methods of desensitization may be specific or non specific The former is passive when the responsible allergens are avoided or eliminated active when the tolerance of the patient for these allergens is increased this may be done orally or by injections

Preparation of a trial diet should be based on (1) the omission of foods to which the patient has shown intolerance data obtained by question ing the patient regarding his diet (2) the elimination of foods giving positive intradermal tests and (3) the omission of foods known to be harmful to the patient in view of his organic condition This trial diet should be accompanied by dietetic cooking i e the manner in which to prepare the foods which varies from one patient to another depending on the condition of the liver stomach intestine kidneys etc should be accurately explained

As this diet is to be followed for only a short time there is no need to be concerned with balancing it

When this basal diet results in the disappearance of the status asthma ticus foods are added to it one by one beginning with the least aller genic foods and continuing to omit foods causing intolerance and other reactions stated by the patient each food being given for four days while the patient is observed to detect the appearance of any symptoms of asthma By this method a diet is prepared which must be balanced from the point of view of carbohydrates fats and proteins as well as from that of salts and vitamins as it will have to be taken over a pro longed period By a diet of this type the foods that actually cause the asthma may be determined

When designing a diet and eliminating certain foods not only should the food or foods to be omitted be accurately defined but the way in which to avoid these foods should be carefully explained This may be illustrated by a case in point when stating that wheat must be omitted this should be amplified by defining wheat as including white and brown bread biscuits semolina vermicelli pastes coffee desserts hard biscuits etc Thus we will not run the risk that the patient will eat the prohibited food out of ignorance and therefore one should proceed likewise with any other food

We believe that diets should be designed in this way We believe standard diets to be useless

Whenever a food is allergenic and also essential we aim at oral desensitization by progressively increasing doses of the food thus attempting to increase tolerance for the latter This method frequently fails

In addition the patient is advised to avoid inhalants which he obviously cannot tolerate or for which he has positive tests as well as those known to be highly allergenic Contact with animals such as dogs cats horses and with feathers wool carpets made of cowhide and lambskin etc should be avoided Here as in the trial diet once all inhalants have been eliminated we request the patient to get into contact with them one by one when his position or occupation compels him to do so and the result is observed

Methods to avoid house dust sweeping with a moist broom or rag Careful daily cleaning of the patient s bedroom the floor furniture etc Avoid carpets pictures curtains many pieces of furniture in the bed room The patient is requested to undress in another room Once a week the furniture is taken out taken apart and carefully cleaned

Septic foci any septic focus whether tonsillar dental sinusal appendicular vesicular etc should be removed

Non specific desensitization Complicated cases of asthma with a yellowish sputum in which a bacterial allergy is probably involved are inoculated with stock vaccines of the Delbet broth type the initial dose being 0 05 ml thrice weekly which quantity is increased with each injection up to a dose of 1 ml Autovaccines

Attention should be drawn to the fact that a recurrence of the attacks caused by the first injections is evidence of the effectiveness of the vaccine

0 50 g of Armour or Whitte s peptone are given orally one half—one hour before meals Daily doses of 0 1—0 3 ml of a 50 per cent solution are administered intradermally for 15—20 days Doses of a 5 per cent solution increasing progressively from one half to 5 ml are injected intravenously at intervals of 2—3 days Doses of a 7 5 per cent solution increasing progressively from one half to 10 ml are injected intramuscularly at intervals of 2—3 days

Autohaemotherapy consists in the injection of doses increasing progressively from 5 to 10 ml every 48 hours A 10 per cent solution made up of equal parts of ordinary syrup and water of sodium hyposulphite is administered orally in doses of 2—4 g daily Two g daily or every 48 hours of a 20 per cent aqueous solution are injected intravenously

Doses of 1 g of magnesium hyposulphite are injected intramuscularly (10 ml of a 10 per cent solution)

Methods acting on the product of the allergic reaction the union of

the allergen with the reagin (antigen antibody reaction) results in the liberation of a histamin like substance H substance or released sub stance which is the agent ultimately responsible for the allergic reaction in the organ of shock the bronchi in this case

There are three methods of acting by increasing histamin tolerance by administering the inactivating enzyme i e histaminase or by giving synthetic antihistaminics

Histamin as a rule acid histamin phosphate diluted in a physiologic saline solution until the intradermal swelling due to 0 02 ml produces no reaction or only a minimum reaction is used Of this dilution doses progressively increasing by 0 02 ml with each injection are injected for an average period of one day until 1 ml has been administered When no appreciable therapeutic results have been obtained a less strong dilution is used the intradermal test being constantly made at the be ginning of each series To avoid possible constitutional reactions we recommend the following method induce an intradermal swelling prior to each dose wait 10 minutes and when it is equal in size or slightly larger than the previous swelling the rest of the dose is injected sub cutaneously when it is very marked the rest is not injected and the dose is repeated with the next injection invariably with the same pre caution

We apply this standard to all desensitizations and thus have been able to avoid constitutional reactions which we have never observed during the 10 years in which we have been engaged in this specialism

We always insist that the physician should prepare the dilutions from a given histamin and that commercial microdose preparations should not be used

Histaminase is an enzyme destroying histamin present in the organ ism especially in the intestine liver and kidneys It may be given orally or intramuscularly for a considerable period without any or only moderate results being obtained

We employ a personal method consisting in the ionization of hista minase We had our most extensive experience in lesions of the skin in wich we obtained considerable results Papers on this subject have been published in the April 1945—141 and November 1945—149 numbers of El Dia Medico Uruguayo

The following method was used the positive pole moistened with water was placed on the posterior part of the thorax and the negative pole with the 1 g per 500 solution of histaminase on the anterior part of the thorax with a milliamperage ranging from 1 to 3 during half an hour The usual ionization apparatus was employed

We are collecting data for future publication but without fear of being mistaken we can state that it is a useful and effective method We were

able to control asthmatic attacks by ionization for half an hour in various cases

Symptomatic medical treatment with adrenalin ephedrin and aminophyllin has been described previously

Benzedrine a sympathomimetic drug stimulating the function of the brain is administered orally after breakfast in doses of 10—20 mgm

Calcium chloride is a substance widely used in allergic conditions though not on a very scientific basis as it has never been possible to obtain conclusive evidence of a decrease of the blood calcium in allergic subjects It may be given orally intramuscularly or intravenously and we shall not enter into a discussion of the correct dosage, as it is generally known

Iodides increase the fluidity of the sputum They also have an effect on fungi The dosage of potassium iodide is 3—4 spoonfuls of a 6 per cent solution daily

Aspirin prior to administration an examination should be made to determine whether the subject is not allergic to the drug, it is administered in doses of 1 g 3 g being given daily

Hormone preparations thyroid and ovary They are used in cases in which they have been found to be involved

Vitamins especially vitamins D and C

Physical therapy ultraviolet irradiation diathermy X ray therapy

IN CHILDREN

To suppress attacks on the appearance of the first symptoms

1) Put the child to bed

2) Administer ephedrine tablets or a preparation composed as follows

Codeine sulphate	0 25	g
Ephedrin sulphate	0 40	g
Glycerin	2	drops
Syrup of cherry q s	120	ml

A teaspoonful every 4 hours in children aged 3 or over the dose is adjusted to age in younger children 0 25 g of syrup of ipecac may be added to the above preparation

3) Nose drops consisting of a slightly vasoconstrictive substance (ephedrin or neosinephrine) the child being placed in a dorsal or lateral position with the head lowered

4) Heated inhalations Not to be used in summer time or when they are unpleasant to the child

5) Aminophyllin in the form of suppositories 0 025—0 050 g in 3 year old children If the child is sensitive to chocolate the suppositories must not contain cocoa butter Small quantities of barbiturates may be added to the suppositories

6) Adrenalin by aerosol in concentrations of 1 1000 or 1 100 depending on the age of the child

7) Injections of adrenalin if everything else fails

Attention should be drawn to two very important things (1) the injection should not be postponed for too long a period to prevent the crisis from being established in a permanent form and (2) an incorrect dosage should be avoided it is advisable to administer the smallest possible doses of adrenalin to ensure an antispasmodic effect and to prevent side effects (nervousness tachycardia tremor etc) A 1 1000 aqueous solution of adrenalin is employed

Status asthmaticus, hydration Intravenous injections of 0 0006 g of aminophyllin per kg body weight

Oxygen tent first make sure that the child does not suffer from claustrophobia

Administration of antihistaminics is not advisable in status asthmaticus as they dry up the bronchial secretions

The failure of treatment with adrenaline in status asthmaticus is due to the fact that it has a bronchodilative action it does not remove the obstruction of the bronchi by secretions These cases should be treated with syrup of ipecac $\frac{1}{2}-1$ teaspoonful being given every hour to induce vomiting and in addition tepid water which also promotes vomiting the asthma being relieved by (1) reflex coughing (2) ciliary action and (3) waves of movement a type of peristaltic The cough acts upon the upper portion of the respiratory tract the ciliary action at a lower level on the finer bronchi and the peristaltic evacuates the respiratory tract

ACTH and cortisone

Two teaspoonfuls of ether in 30–60 g of oil per rectum Also potassium iodide belladonna lobelia and stramonium

MOLD ALLERGY*

by

HOMER E PRINCE

Airborne molds are now accepted as a common cause of respiratory allergy The ordinary airborne mold population arises from sources in outside environments such as soil decaying vegetation etc Special environments on the other hand such as damp cellars luggage fruits and even upholstered furniture can be definite sources of mold contact in particular instances

Two methods are available for identification of airborne mold spores The first or the pollen slide method is rapid and gives data comparable to pollen counts However molds of only a few genera including Hormodendrum Alternaria Fusarium Helminthosporium and Spondylocladium and occasionally smuts and rusts can be appreciated by the slide method The culture plate method which employs some form of selective media for the growth of molds is more suitable for the identification of a much wider variety of molds Exposures can be made for short periods depending on anticipated incidence I have ordinarily employed the two minute exposure time With the cooperation of a trained mycologist all culturable molds can be determined even to species identification by the culture plate methods Certain molds particularly of the Basidiomycetes group which group includes the smuts and rusts cannot ordinarily be appreciated even by this method

In general molds are distributed throughout the entire United States In the southern areas molds present perennial problems while in the north counts are much lower through the winter months In general species of the *Dematiaceae* particularly *Alternaria* and *Hormodendrum* make up the greater percentage of molds found in ordinary survey studies in most areas This is particularly true in the central and southern areas West of the Rocky Mountains Alternaria and Hormodendrum are of somewhat less importance than in other areas In special environments plate identification is often necessary to appreciate the true mold picture

* The subject of mold allergy is quite broad and now embodies a sizeable number of articles in the medical literature It is not possible for me to undertake any references to previously published articles on mold allergy in this abstract Furthermore it is with considerable humility that I attempt to write such a brief and incomplete article on mold allergy for a meeting in Holland where so much of the pioneer work on molds has been done by the late Dr STORM VAN LEEUWEN and his confreres including Dr VAN DER WERFF and the late Dr KREMER

The following list represents the author s selection of molds for ordinary testing and treatment This selection is based on survey findings over a period of several years

PHYCOMYCETES
- *Rhizopus nigricans*
- *Mucor racemosus*

FUNGI IMPERFECTI
- *Dematiaceae*
  - Alternaria tenuis
  - Curvularia spicifera
  - Spondylocladium sp
  - Helminthosporium interseminatum
  - Hormodendrum cladosporioides
  - Stemphylium botryosum
  - Nigrospora sphaerica
  - Pullularia pullulans
- *Moniliaceae*
  - Aspergillus
    - fumigatus
    - flavus
    - glaucus
    - nidulans
    - niger
    - sydowi
    - terreus
  - Botrytis cinerea
  - Gliocladium fimbriatum

FUNGI IMPERFECTI (Ctd)
- *Moniliaceae* (Ctd)
  - Monilia sitophila
  - Mycogone nigra
  - Paecilomyces varioti
  - Penicillium
    - atramentosum
    - biforme
    - carmino violaceum
    - intricatum
    - luteum
    - notatum
  - Trichoderma viride
- *Sphaerioidacae*
  - Phoma herbarum
- *Tuberculariaceae*
  - Fusarium vasinfectum

ASCOMYCETES
- *Saccharomycetaceae*
  - Saccharomyces cerevisiae
- *Torulaceae*
  - Rhodotorula sp
- *Chaetomiaceae*
  - Chaetomium sp

It is to be noted particularly that in this list molds are arranged according to their botanical classification

Mold extracts may be prepared by the allergist for his own use if he so desires The simplest method for practical preparation of extracts for local environments is to expo e the petri dish charged with Sabouraud s medium for fifteen minutes and inoculate at room temperature After the molds reach maturity which frequently requires three or four weeks the petri dish may be filled with an appropriate extraction fluid such as Hollister Stier solution and the extraction carried out for 24 hours At the end of this time the extraction fluid is decanted and sterilized by Seitz filtration A more appropriate method for the preparation of extracts is to inoculate identified cultures into liquid medium contained in Erlenmeyer flasks A suitable medium for this purpose is malt extract broth obtained from the Difco Laboratories in Detroit After the pellicles

reach maturity they may be removed dried then extracted on a weight volume ratio in the usual manner More recently type 33 mold extracts developed by The Association of Allergists for Mycological Investigations Inc have been made available commercially by the Hollister Stier Laboratories These extracts are very potent and possess great specificity with a minimum of nonspecific irritating qualities

Testing with mold extracts is ordinarily carried out in much the same manner as other inhalant substances such as pollens are tested Scratch tests with the type 33 molds are essential as a preliminary step, negative reactions may be confirmed with 1 1000 intradermally Positive reactions by scratch tests should be followed with higher dilutions intradermally often up to 1 100 000

Positive mold reactions are significant if they are obtained by the scratch technique if they are obtained in high dilution by intradermal testing and if they are confined to botanically related molds Systemic reactions following intradermal tests and finally beneficial results with treatment enhance the significance of mold reactions

DISCUSSION

P J VAN DER WERFF

May I remind you of the fact that Dr Prince is one of the pioneers of fungus allergy in America he was the first in the world to draw attention to non pollen cau es (viz. molds) in hayfever to the occurrence of seasonal mold allergy etc

Perhap you will be interested to learn how conditions are here in the Nether lands

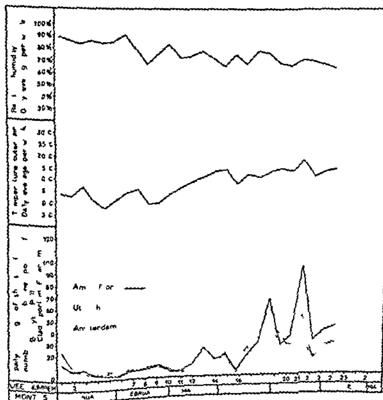


Fig 1

First I must emphasize that each country has its own dominant mold groups outdoors and indoors So the allergologist who is interested in mold allergy should carry out his investigations on fungi in his own environment

In Holland the whole year round there are variable accounts of airborne substances of fungi in the open air table I shows the cultivable moulds prevailing here in Utrecht

TABLE I

In Utrecht the counts for one year were 6345 cultivable moldspores Duration of exposure 5 hours a month

Bernstein & Feinberg method	
Cladosporium	31 4 %
Fusarium	7 6 %
Botrytis	3 1 %
Pullularia	2 5 %
Penicillium	30 6 %
Yeasts	21 0 %
Mucor	2 0 %
Alternaria	0 4 %
Mycelia sterilia	0 3 %
Trichoderma	0 27 %
Aleurisma	0 25 %
Other Fungi	
33 colonies of 13 genera	

Many fungus colonies in the first stage growing as Mycelia sterilia were found to be Fusarium species when a correct cultivation technique was used acid oatmealagar rice stalks of the Lupinus polyphyllus Lindl

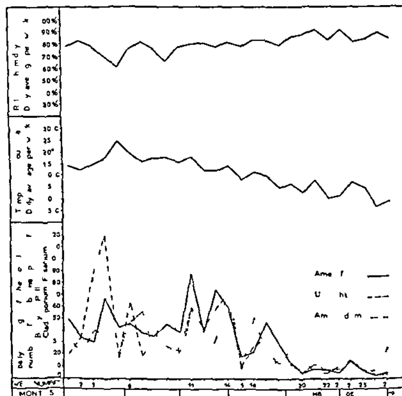


Fig 2

No connection with weather or seasonal influences could be demonstrated regarding 2 of the dominant groups yeasts and Penicillia

But the occurrence of the air borne spores of a group of 4 dominant genera viz Cladosporium (Hormodendron) Fusarium Botrytis and Pullularia is remark able showing characteristic peaks during summer and autumn (fig 1 and 2)

As can be demonstrated this fact largely depends on the temperature and relative humidity of the atmosphere outdoors

The highest peaks are mainly observed when the average daily temperature is 10 C and over and the average humidity is 75—100 per cent

During that period there is an increase in the frequency and intensity of acute attacks of asthma some patients being subject to attacks during that time only others being liable to particularly severe attacks during this period but showing minor disturbances throughout the rest of the year These patients showed a specific mold allergy coinciding with their seasonal periods of allergic mani festations of the respiratory tract Inclosing I wish to say to those amongst you who have a special interest in this field that the Mold Culture Centre (Centraal Bureau voor Schimmelcultures) Head Prof Johanna Westerdijk & her associates a o Dr G A de Vries Javalaan Baarn Holland will give any information and supply any wanted mold culture for comparison etc

THE RELATION OF PARTICLE SIZE TO THE ALLERGIC REACTION OF THE BRONCHI

by

K MAUNSELL

Inhaled particles larger than 100 microns in diameter are caught by the vibrissae and expelled Particles of a diameter of 100 to 10 microns will be deposited in the nasal fossa pharynx and trachea Into this category fall all pollens and larger spores and clumps of spores and medium sized dust particles to which bacteria may be attached Particles of a diameter of 10 to 3 microns will be deposited mainly in the bronchi and bronchioles In this range are included smaller spores such as Penicillium and Cladosporium and smaller dust particles Once inhaled these particles cannot be exhaled because deposition takes place They are re moved by ciliary action and ultimately swallowed or expelled by sneezing and coughing Whilst they are travelling on the conveyor belt to the nasopharynx the fully water soluble allergens are dissolved and can react locally with the mucous membrane of the upper and lower respiratory tract Only particles less than 3 microns in diameter such as bacteria and fine coal dust, reach the alveoli and are exhaled in varying degrees or eliminated by phagocytosis

References

DAVIES C N (1945) *Brit J Indust Med 6* 245 — *Id 9* 120
MAUNSELL, K. (1955) *Proc d R.S.M Section Lary gol 48* 9

TREATMENT OF ASTHMATIC PATIENTS DURING OPERATIONS

by

W J QUARLES VAN UFFORD

There are various sides to the surgical treatment of patients with bron chial asthma

I There is a favourable side ether is a favourite drug in the treatment of severe cases of status asthmaticus which fail to respond to any other form of therapy the antibacterial agents administered frequently have a favourable effect on the existing bronchitis the operation may be regarded as a stress which may have a favourable action

II There is an unfavourable side symptoms of hypersensitiveness to procaine etc (treatment of headache with aspirin) administration of opiates to relieve pain increased bronchitis due to singing cough reflexes especially those due to the temporary limitation of respiration postoperative aggravation of the symptoms of asthma (attributable to a lowered general resistance impaired ventilation of the lung (possibly associated with bronchitis) administration of drugs change from rest to motion change from surroundings free of dust to surroundings con taining large quantities of dust after discharge from the hospital)

In view of the adverse action on the recovery from the effects of operation *prevention* of attacks of asthma bronchitis etc is indicated in these cases This implies pre operative treatment of possible un favourable reactions which may be expected to occur

Often the two methods of treatment coincide in part

phenergan is frequently used in premedication in modern anaesthesia phenergan may often be used effectively to treat insomnia due to pain or even to relieve pain One ml is administered initially in these cases and if need be another ml is given one week later

Administration of blood and fluid by intravenous drip enables us to give aminophyllin and if necessary some procaine throughout the entire day

Antibacterial treatment often is very useful not only to prevent in fections in the operative field but also to avoid possible exacerbations of the bronchitis Treatment is preferably started shortly prior to operation

In addition the patient is given pre operative treatment in an attempt

to eliminate the symptoms of bronchitis and asthma postoperative treatment consisting in administration of expectorants (twice a day ½ hour of treatment with steam frequently affords considerable relief) to keep the chest as loose as possible administration of anti asthmatic drugs in the form of suppositories if necessary and administration of aminophyllin (combined with procaine if need be) by intravenous drip

Personally I was much impressed by the treatment of surgical patients with breathing (and other) exercises in the Physiotherapeutic Department of the Brompton Hospital as this treatment also increases ventilation This method has not yet been generally adopted in the Netherlands This must be estimated very important

Accordingly the following scheme of treatment is indicated

a) avoid any unnecessary drugs (e g aspirin)

b) substitute phenergan for morphine etc

c) to prevent possible allergic reactions to drugs administer powerful antihistaminics when giving premedication (also administer these antihistaminics during antibacterial treatment)

d) prevent and if necessary rapidly treat symptoms of bronchitis
   1) increase ventilation
   2) antibacterial therapy
   3) administration of expectorants etc

e) prevention of asthma by medical treatment often is much easier than the suppression of attacks Therefore some aminophyllin (possibly included in the intravenous drip) should be given during the first days

f) to increase the breathing after the operation inhalation therapy with 5 per cent carbon dioxide with oxygen may be useful during the first 24–28 hours several times a day

This method of treatment was effectively used to prevent the appearance of symptoms before during and after operation in almost all cases

HOSPITALIZATION OF ASTHMATIC PATIENTS

by

W J QUARLES VAN UFFORD

Treatment of asthma has a twofold object

I suppression of the current attack

II prevention of further attacks

A patient with bronchial asthma may be hospitalized for

a status asthmaticus

b) a chronic bronchial asthma in which a detailed clinical examination is advisable in view of the accessory symptoms

c) a chronic bronchial asthma in which the attacks of dyspnoea follow one another in rapid succession

d) examination to determine the degree of disablement

e) tests for certain allergic factors (district house allergens diet tests psychological and social examination)

The attacks can usually be controlled by rest the change of surroundings administration of ACTH euphyllin adrenalin etc In that case the first object will have been attained

The examination will also lead to conclusions regarding a possible cardiac therapy treatment of focal infections revealed by examination etc

The time will come however when the doors of the hospital are opened wide again and the patient can return home or go to another climate or a convalescent home This is the time when those who have only had eyes for the successful suppression of the attacks or the results of the examination meet with a great disappointment outside the hospital at the station in the motor car during the first night at home or even later the symptoms often recur in the most severe form if they have not been aggravated which frequently results in another hospitalization and great disappointment to the patient

Therefore we personally use the following method

If necessary the social worker employed in my practice tries to establish contact with the patient and his family during the period of hospitalization to attempt to remove possible difficulties

Secondly when leaving the fact is stressed to the patient and his family that hospitalization does not imply that the satisfactory condition will also persist after he has left When he has been given more detailed information regarding the nature of his disease in advance his disappointment and therefore possible reactions will be less severe

Thirdly the factors that will be a danger to the patient after his discharge should be determined as soon as possible after hospitalization

a) hypersensitiveness to house dust

b) other environmental allergens (fungi factory dust animals etc)

c) dietetic errors (particularly liable to occur when the patient is in very good health)

d) the change from more rest to more exercise

Therefore treatment during the period of hospitalization is not only medical and generally roborant but also consists in

a) rapid desensitization by the house and occupational allergens, as a preliminary to the prolonged treatment at home In some cases we start with a scheme of injection in which injections are given every 4—5 hours on the first day every 6 hours on the second every 8 hours on the third every 12 hours on the fourth and then once daily the intervals between the injections being gradually prolonged

b) vigorous breathing exercises and kinesitherapy

In addition we try to accustom the patient to his own surroundings as smoothly as possible patients never return home directly from their beds We almost always observe a scheme of mobilization in which the patient is allowed up in the ward for about two days then is allowed to walk in the corridors then allowed out of doors for a moment then allowed to walk out of doors then allowed longer walks out of doors and then allowed to visit his home he has tea at home rests at home for a moment has a meal at home (often a more or less severe sense of constriction or dyspnoea occurs the first time and also the next evening and night) then goes home for half a day or a day and finally is discharged from the hospital Disappointments are much less frequent in this case Moreover in severe cases of dust allergy etc we proceed on the assumption that the change from an environment free of dust to one containing large quantities of dust will cause disturbances so that during the first weeks we give the patient additional treatment at home with aminophyllin (especially suppositories) and antihistaminics In some cases the patient returns for some time to be given a gradually decreasing aerosol treatment with aleudrin and theophyllin

We also use this scheme of adjustment after a period of [illegible] following high altitude and other methods of treatment

In these cases the patient also is frequently disappointed as symptoms recur when he is walking about the garden or during the first days at home so that we advise starting desensitization during the stay in the mountains followed by medical treatment during the period of transition

We believe that this scheme of treatment offered considerable advantages in our patients

Reactions during the period of transition were highly exceptional whereas otherwise they were a common feature in these cases

A CRITICAL VIEW OF THE TREATMENT OF BRONCHIAL ASTHMA

by

VLADIMIR SPUŽIĆ VOJISLAV DANILOVIĆ AND SLOBODAN VUKOBRATOVIĆ

On the basis of twenty years experience of treating nearly 6000 cases of asthma we have noticed what has already been pointed out by some others that while in some cases we are able to interrupt the asthmatic attacks in other instances our results are uncertain in spite of our therapeutic measures This is in accordance with the fact that asthma is not a definite disease but a syndrome provoked by various causes (Bezançon [1] Pasteur Vallery Radot [2] Frugoni [3] etc) and that even the reaction the asthmatic attack is composed of several elements (bronchospasm oedema hypersecretion) combined in a very different way in each particular case Consequently this condition is but the result of various etiologic factors

Asthma is most frequently a disease of allergic character the results of antigen antibody reaction although it can be non allergic in character However these two mechanisms are very often combined or substituted

I ALLERGIC ASTHMA

According to the majority of writers (Frugoni [4] 44 5 per cent Castex [5] 64 9 per cent Duchaine [6] 100 per cent) allergic asthma is of most frequent occurence In its mechanism which is generally very complex one can distinguish three phases sensitization production of the shock tissue and the onset of the attack Each of these phases depends on a great number of factors The quantity of the allergens the contributary and localizing factors as well as the constitution of the organism are of special importance For the determination of the shock tissue and the declension of the attacks of already sensitive patients some other factors are also of great importance the place and method of the penetration of the allergens into the system the injury of the tissue the condition of the shock tissue and different external causes (sudden metereological changes lesion of the mucous membrane of the bronchial tube by an infective agent or intoxication) and other factors Because of a different pathogenesis in particular cases it is important to determine the role of each of these factors before the necessary treatment is undertaken

a) The quantity of allergens i e constant exposure to allergens as is well known is of great importance in the sensitization of the

organism and in the onset of asthma The purpose of many methods of treating asthma is to influence this factor

1) The elimination of harmful allergens (dust fog drugs)

2) The reduction of harmful allergens (improvement of housing conditions and workshops and the sanitary improvement of the environment etc) The isolation of the patients from a harmful environment (by change of environment change of profession etc) If we wish to obtain lasting results it is necessary to apply all these methods for a long time which is not always easy These methods usually give favourable results but in the case of a definite predispostition the results are less favourable since the patient is quickly sensitive to the allergens of a new environment

b) The contributary factors which by injuring the mucous membranes of the bronchial tubes facilitate the penetration of allergens and consequently sensitization are very important in the onset of an attack of asthma Dust sudden changes of temperature harmful evaporations etc are of great importance in occupational asthma humidity fog in low lying regions, winds as well as poor hygiene and housing conditions are important in the incidence of asthma in regions which are conducive to allergy The elimination of such factors plays an important role in the treatment of asthma In that sense the following measures should be applied the improvement of the sanitary conditions of workshops and houses change of profession appropriate climatic treatment etc

c) The importance of localizing factors upon which depends the localization of the allergic reaction, has been pointed out in many experimental works by Vaubel Gudzent Halpern [7] Spužić [8] as well as in the clinical observations of Bezançon [9] Frugoni [10] Danielopolu [11] and Jacquelin [1] The localizing factors are as follows the way of the penetration of the allergen and all other factors which may injure the mucous membrane of the bronchial tubes (infection gas etc) and cause bronchitis We use different methods for the relief and recovery of the shock tissue antibiotics autovaccines climatic treatment, change of profession etc

d) The immediate determining factors (presence of allergen cold sudden changes of temperature various irritative gases railway engine smoke) are of great importance in the onset of an attack These factors which are often both contributary and localizing are often favourably influenced by improvement of hygiene climatic therapy change of profession change of locality etc

e) Constitution is of prime importance in asthma The factors which influence the terrain are numerous and of first importance heredity (Bray) [13] the condition of the neuro vegetative and endocrine system (Maranon) [14] lowered inborn resistance of certain tissues (Djuričić) [15] (Parrot) [16] (Frugoni) [17] and the disturbance of the metabolism of the

histamine It is uncertain whether the terrain is actually formed during the evolution of the disease Coope [18] believes that the terrain undergoes changes in the course of life and that it is strengthened or weakened The treatment of the disturbance of the neuro vegetative and endocrine systems and climatic and balneologic treatment have a considerable influence on asthmatic patients Since many factors in combination are involved in the determination of asthmatic attacks the treatment of asthma cannot be simple or schematic

THE VALUE OF VARIOUS METHODS OF TREATING ALLERGIC ASTHMA

In the treatment of allergic asthma the following factors are of great importance the elimination of the harmful allergen specific desensitiza tion and the elimination of contributary and localizing factors

The elimination of harmful allergens and the isolation of the patients from a harmful environment

In some rare instances of allergic asthma where sensitization to one allergen only is present (horses cats flour ipecacuanha) after the elimination of the corresponding allergen the asthmatic attacks stop After prolonged non exposure to the harmful allergen the cessation of the attacks can be permanent Later unfortunately due to the individual constitution the body may be sensitized to some other allergens and the attacks may reappear More frequently where there is sensitization to a great number of allergens this method is difficult to apply and the results are less satisfactory When the patient is sensitized to a greater number of allergens and there is no possibility of the elimination of all these allergens similar satisfactory results can often be obtained by removing the patient from a harmful environment (by change of resi dence profession region etc)

Eliminatory diets improvement in sanitary conditions climatic treatment children s homes change of profession etc have such an effect In general all these methods are satisfactory due to their lack of the corresponding allergen The prolonged absence of an allergic reac tion leads to the relief and eventually to the healing of the shock tissue This method of treatment is the most simple and usually gives rapid and satisfactory results which unfortunately are not often lasting or perma nent if the remaining harmful factors are not treated at the same time

Specific desensitization

The specific desensitization by which one can attain the state in which the organism shows no reaction in the presence of the corresponding allergen is of great importance in the cases in which it is impossible to eliminate the harmful allergen This is one of the most reliable methods and actually it is the only method of treating allergic asthma

Out of 237 cases which were under our treatment and were followed for two years or more ([19 0 1]) satisfactory results were obtained in 48 9 per cent of the cases Similar satisfactory results were obtained by some other writers For instance Bruun [2] has also obtained satisfactory results in 59 8 per cent of the cases of asthma which he followed for a period of from 3 to 5 years The satisfactory results which are usually obtained by means of specific desensitization are often temporary (1—3 years) and seldom of long duration or permanent Much better results can be obtained when desensitization is prolonged or repeated According to our experience the success of specific desensitization depends on the following factors the treatment should be begun as early as possible in the early stages of asthma it should be carried out without interruption for a sufficiently long period and in respect of all the allergen to which hypersensitization exists at the beginning of the treatment the patient should at least for a certain time be isolated from the harmful environment At the same time any bronchitis which may facilitate the penetration of the allergen into the organism should be treated Better results can be obtained from specific desensitization in cases where there is hypersensitization to one or to a limited number of allergens

The mechanism of the action of specific desensitization has not yet been fully explained Most writers consider that specific desensitization increases the quantity of the antibodies whilst Pasteur Vallery Radot [3] believes that only a temporary accomodation to the harmful allergen can be obtained by this method

The rush desensitization is more quickly effective but is frequently followed by untoward reactions

The elimination of contributary factors

The elimination or reduction of contributary factors (humidity dust smoke factory gases etc) generally has a favourable effect on the bronchial mucous membrane and thus diminishes the possibility of the penetration of allergens to the sensitized tissues

The contributary factors can be modified by a number of methods improvement of hygienic conditions in workshops houses and locations change of profession climatic treatment residence in institutions for asthmatic people etc as well as by the application of antibiotics

The favourable influence of an improvement in hygienic conditions and change of harmful environment is a matter which will be discussed in the following chapter We shall now examine the part played by antibiotics Their significance has been more strongly emphasized in recent times

The mode of action of antibiotics is a scomplex as is that of the bacteria on which the antibiotics act The antibiotics (penicillin terramycin

aureomycine) through their effect on bacteria reduce or eliminate the harmful antigen in cases where sensitization to bacteria exists while in other cases they act on bacteria which are contributary or localizing factors In 550 cases of asthma which were treated with antibiotics favourable results were obtained in the majority of cases Especially good results were obtained in asthmatic children (79 per cent) [4] while the results obtained in adults where chronic changes of the bronchial tubes still existed were found to be less satisfactory (65 per cent) [25] In accordance with the results of Findensein [26] we have obtained better results in cases in which aerosol treatment was applied According to our experience as has been stated by Pasteur Vallery Radot [27] the best effect of antibiotics was noticed when they were administered during Spring or Autumn when bronchitis occurs most frequently Unfortunately the favourable effect of antibiotics is usually of short duration and lasts only while they are administered or for some months after the discontinuance of the treatment As the favourable effect of antibiotics is of short duration they should be used at the first onset of the infection of the respiratory organs and in all early cases of asthma The treatment with antibiotics should be repeated and if necessary combined with other methods of treatment e g autovaccin Thus we succeeded in preventing the onset of asthma for many years in some cases However this means that they usually constitute only a supplementary treatment

The elimination of localizing factors

The elimination or reduction of localizing factors which are often the same as contributary factors but of much greater intensity can reduce the sensitivity and can sometimes lead to the recovery of the shock tissue Many of the above mentioned methods of treatment may lead to these results sanitation climatic treatment vaccines antibiotics etc

a) Sanitation is of great importance in solving this problem The experience accumulated during our studies of allergic patients who were working in various factories (silk [28] stuff [29] asbestos [30] glass [31] tobacco rubber and leather [3] etc) shows that humidity and sudden changes of temperature have a decided effect on the onset of asthma and that the elimination of these factors contributes to the disappearance of asthma This is best illustrated by the fact that all the women workers in one spinning mill who often fell ill with bronchitis and asthma while working in premises with a high temperature and a high humidity had no more attacks as soon as they left these premises although the causal silk allergen was present in abundance We have also established that sanitation (canalization [3] and the construction of dams against floods) [33] have a very favourable effect on the reduction of asthmatic cases in these regions

b) Climatic treatment (sea and altitude) have also a good effect on the elimination of harmful allergens and on environmental factors such as fog dust humidity, winds etc With the disappearance of allergic reactions the shock tissue recovers sometimes so well that later it does not react by asthmatic attacks to the presence of the causal allergen Blaumoutier [34] Pasteur Vallery Radot [3] and Turban [36] Spengler and others have established the favourable effects of a high altitude climate which is confirmed by our experience The high altitude climate has an especially good effect if certain conditions are fulfilled the localities must be protected from winds fog etc The climate of the Dalmatian coast has a similar favourable effect In 653 cases of asthma in children [37] and in adults [38] we obtained especially satisfactory results in 75 per cent *of the cases treated on the Dalmatian coast Unfortunately in most cases* this favourable result was not of long duration The effect of the sea and a high altitude climate is much more effective in early cases of asthma and when the climatic treatment has lasted for a longer time at least for some months

c) Balneologic treatment in addition to the fact that it acts in the same way as climatic treatment by removing the allergen and relieving the shock tissue has a favourable and direct effect on the effected tissue of the bronchial tubes as has been established by Villaret Bezançon [39] Santenoise [40] etc

d) The effect of vaccines and autovaccines and many other treatments of asthma chimotherapy antibiotics etc is complex In some cases the autovaccine causes specific or non specific desensitization Further by its action on chronic changes of the bronchial tubes as a stimulating treatment it decreases the effect of contributary and localizing factors

The satisfactory effect of vaccines and autovaccines has been stressed by many writers (Haibe [41] Harley [4] Božovic [43] while Diaz [44] obtained a favourable effect in 63 per cent cases we had only 48 per cent satis factory results in 380 cases of bronchial asthma which were treated with autovaccines But in most of these cases these favourable effects were of short duration a few weeks or months and rarely for a longer period—two years or more—and total recovery was obtained only in a limited number of cases Since this favourable reaction is often only temporary the autovaccine should be repeated especially in the autumn as has been already suggested by Pasteur Vallery Radot and Blaumoutier As exclusive treatment with autovaccine is usually insufficient it is necessary to combine it with other methods of treatment (antibiotics etc)

As one can see all the above mentioned methods of treating asthma do not have a favourable effect in all cases However the favourable effect is in most of these methods only temporary Since these methods

give satisfactory results in early cases it is necessary to start the treat ment as soon as possible and to apply it systematically by combining the above mentioned methods of treatment

II NON ALLERGIC ASTHMA

This group includes all cases of asthma which are not proved to be of allergic nature It is uncertain whether all cases of asthma belonging to this group are caused by the same mechanism, Dowall [45] has shown that bronchospasm can be caused by various stimuli irritation by gases (CO SO_2 etc) changes in potassium calcium and the other blood electrolytes direct irritation by histamine or peptones as well as by reflectory or psychical stimuli Nevertheless the mechanism of an asthmatic attack has not yet been precisely established In non allergic asthma the important factors are bronchospasm oedema and hyper secretion of the mucous membrane of the bronchial tubes In allergic asthma as we have seen these changes are determined by an antigen antibody reaction i e H substances which result from this reaction According to Rackemann [46] H substances have an effect in non allergic asthma also Actually the action of H substances is very complex and insufficiently studied Some writers consider that H substances have an effect on the capillary permeability smooth muscles and bronchial secretions in non allergic asthma also Dowall [47] has shown that with the reduction of sodium in the cells as occurs when there is insufficient adrenal cortex the smooth muscles become sensitive to histamin According to Stern [48] histamin has an action mainly on the cells which contain much diaminooxidae which is later the recipient for histamin Parrot [49] found that the serum of an asthmatic patient has a lowered histaminopexic power i e it does not absorb the histamin which reaches the blood On the basis of the above mentioned facts one could suppose that the increase of histamin in the blood has a stimulating action on the cells of the tissues which contain more diamonoxidae However although all this points to the importance of H substances, the mode of their formation and action has not yet been definitely settled Besides it is uncertain whether H substances play a role in all cases of non allergic asthma perhaps this kind of asthma is caused by some other mechanism According to many writers (Danielopolu [50] Santenoise [51]) in non allergic as well as in allergic asthma the local distonies of the neuro vegetative system play an important part while some writers (Dowall [5] Serafini [53]) consider that changes in the electrolytes of the plasma play an important part by their direct action on the neuro vegetative system and the smooth bronchial muscles However the possibility cannot be excluded that even in these cases the changes

are caused by H substances Accordingly it appears that there ought to be no difference between allergic and non allergic asthma

In non allergic asthma the factors which have been mentioned in our discussion on allergic asthma are also of great importance disposition constitution contributary and localizing factors In non allergic asthma as well as in allergic asthma the condition of the neuro vegetative and endrocrine systems and the resistance of the connective tissue are of great importance The contributary factors in non allergic asthma in general are the same as in allergic asthma but here they play a different role instead of facilitating the penetration of allergens they allow the harmful factors to act on the reacting shock tissues The localizing factors with the resulting tissular lesions will determine the tissue which will react in the case of non allergic asthma also

In spite of the fact that the causes and mechanisms which lead to an attack of non allergic asthma are different and in view of the fact that the reaction—an asthmatic attack—is usually more or less the same in all cases it is possible to apply some common methods of treating non allergic asthma

Methods of treating the symptoms of an asthmatic attack

In the cases where we are not able to explain the causes of an asthmatic attack both in allergic and non allergic asthma we must use methods which have in effect on the changes themselves which determine the attack i e bronchospasm oedema and hypersecretion Since the causes which lead to an asthmatic attack are the expression of a local distonism the sympaticomimetic or parasympaticolytic substances may be used with success adrenalin aleudrin ephedrin atropine etc It is known that these drugs are of great value but only in interrupting an asthmatic attack and that their immoderate use can cause an aggravation of the condition

Theophyllin and its derivates have a very favourable effect on asthmatic attacks especially when used with aerosole (Pasteur Vallery Radot) [54]

In 42 per cent cases we have obtained satisfactory results with anti histamine substances [55] which prevent untoward manifestations caused by histamin however Frugoni [56] and Serafini have obtained 40–50 per cent good results and Pasteur Vallery Radot [57] and his co workers in 66 per cent of their cases

In severe asthmatic attacks satisfactory results can be obtained by using hormones ACTH and cortisone In accordance with the results of Pasteur Vallery Radot and his co workers the result we have obtained have proved to be satisfactory In 55 cases of severe asthmatic attacks treated with these hormones in accordance with some other writers we obtained favourable but temporary results in 83 per cent of the cases [58]

The method of action of ACTH and cortisone has not yet been established Quarles van Ufford considers that adrenalin cortex does not play an important role in allergy, and that it acts only on one of the many disturbances of the endocrine glands which exist in allergic conditions

Non specific desensitization
Experience has shown that some substances such as pepton serum, milk tuberculin calcium and magnesium sulphate can have a favourable attack on asthma The mode of their action in asthma is explained by coloidoclassical shock and by a following refractory period However these substances are unreliable and not much used

Pyrotherapy
A temperature artificially provoked by preparations of sulphur, vaccines etc can in some cases stop severe asthmatic attacks (Storm van Leeuwen [60] Vuletic) [61]

Physical treatment
Physical treatment (x rays, ultrasone, ultraviolet rays diathermy) which most frequently acts like non specific desensitization, does not give definite results x ray treatment from which Pasteur Vallery Radot and Blaumoutier [6] have obtained excellent results in 23 per cent of their cases and improvement in 41 per cent has been shown to be of less value in our cases (36 per cent) [63]

Psychotherapy
Although the psychic condition is of great importance in the constitution of asthmatic patients as was stated by Hansen [64] there is actually no asthma of psychic origin According to our experience [65] the asthmatic condition has an influence on the psychic condition of the patient it is obvious that later it can cause an asthmatic attack in the event of an emotional disturbance According to Diaz [66] emotional disturbances as well as sudden metereologic changes can cause an asthmatic attack The results which have been obtained so far with psychotherapy show that this is only a supplementary factor

Surgical treatment
Leriche [67] Goebell Jakovljecić [68] Putnik and some other writers have obtained encouraging results in the improvement of 25–50 per cent of their cases when they used the method of the infiltration of ganglium stellatum stellectomy and some other surgical interventions on the sympathicus This relatively low percentage of favourable results the fact that the indications are not precise and the results of the intervention itself are often unpleasant are the main reasons why the surgical treatment of

asthma is not frequently applied as has been stressed by Leriche in the Second International Congress on Asthma at Mont Dore

The surgical treatment of focal infections (inflamed tonsils sinuses etc) actually belongs to the treatment of asthma based on the elimination of the causal allergen

In non allergic asthma the elimination or reduction of contributary factors—dust humidity fog sudden barometric changes—also plays an important role in the treatment of asthma This can be obtained by climatic and balneologic treatment sanitation housing conditions workshops localities change of residence and profession etc

Conclusion

As has been seen many of the above mentioned methods of treating asthma have a favourable effect in the majority of cases (30 – 60 per cent) In some cases the favourable results can be obtained easily simply by the elimination of harmful objects or the removal of the patient from an unwholesome environment in other cases however they are not easily obtained This favourable effect is in the majority of cases only temporary so that cases of complete recovery are very rare even when the results are entirely satisfactory Therefore even in early and relatively mild cases of asthma and still more in long standing cases it is difficult to see the success of the treatment In this respect it is very difficult to find any other disease which can be compared with asthma This is the explanation of the prevailing opinion that asthma is an incurable disease The uncertain results of the treatment of asthma are mainly due to the great complexity of the mechanisms of this disease and the large number of extrinsic and intrinsic factors which determine the manifestation of early and late asthmatic attacks It has been mentioned already that besides an asthma of allergic nature the mechanism of which is already very complex especially if one takes into consideration the treatment by antihistamines there is also an asthma of non allergic character with different mechanisms where at least in some instances histamin plays an important role The constitution (terrain) which plays a significant role in all these mechanisms has not yet been sufficiently studied The role of many extrinsic factors which play an important part in sensitization formation of shock tissue and the determination of asthmatic attacks is by no means less clear

For these reasons in order to make the treatment of every case of asthma rational and successful it is necessary not only to establish the diagnosis of asthma but also to appreciate the mechanism of an attack and all other factors which co operate in the determination of an asthmatic attack However this is not possible in all cases even in specialized institutions The complexity of the etio pathogenesis of

asthma and the uncertainty of its treatment are the main reasons among others for the scientific discussion of the treatment of asthma and the organisation of associations of specialists in asthma

On the basis of our experience and results which are confirmed by other writers on the treatment of asthma the following general principles are suggested

1) The success of the treatment of asthma as well of other diseases depends in the first place on an early diagnosis and treatment in due time Many latent forms of asthma frequently remain unknown for a long time or they are not at first thought to be serious accordingly a correct and vigorous treatment which if applied at the proper time would lead to more satisfactory results is not applied If systematic treatment is not applied at the beginning mild and reversible changes of the mucous membrane of the bronchial tubes and the local distony of the neuro vegetative system which are followed later by psychical changes in the patient and, finally by permanent changes such as chronic bronchitis emphysema and cor pulmonale may occur Frequently the spontaneous cure of infantile asthma and the favourable results when treatment is applied early justify the fact that the greatest care should be given to the treatment of asthma in children young persons and in general in all early cases of asthma

2) In view of the fact that asthma is but an expression of a large number of different factors the principle of the treatment of asthma must be such as to influence all factors at the same time In this sense for instance we combine the specific desensitization with the temporary removal of the patient from an unwholesome environment and if necessary we treat contributary factors such as bronchitis with antibiotics autovaccines etc These methods are used successively or contemporaneously according to the severity of the asthmatic case

3) Due to the fact that we are never certain of permanent and total cure the treatment should not be discontinued immediately after the first satisfactory results which are only temporary Many of our cases show that the disappearance of asthmatic attacks does not mean that the sensitization has disappeared nor that shock tissue has been cured Under new favourable conditions further asthmatic attacks may supervene after a longer time For this reason even the successful cases should be kept under constant observation and closely controlled and should the slightest signs of aggravation appear vigorous intervention should be undertaken Due to such procedure many cases of severe asthma have been practically permanently cured

Although these three principles in the treatment of asthma are of importance in all cases there are nevertheless some methods of treat

ment which correspond to various ages are of particular importance For instance while climatic treatment relieves all cases in infantile asthma antibiotics are of great value In adults and in occupational asthma besides specific desensitization sanitation is very important In old persons with complicated asthma symptomatic treatment has a special value

From all the above mentioned facts one can conclude that an early treatment of asthma should be continued in which various methods are combined This however is rather expensive Hence an appropriate treatment is in many cases impossible and unfortunately it is usually palliative so that the disease is more and more neglected and difficult to cure

References

1 BEZANÇON F *Ire Congrès Int de l asthme* Paris Masson, 193. 5—41
2 PASTEUR VALLERY RADOT *Comment traiter de l'asthme* Paris Flammarion 1953
3 FRUGONI C MELLI G *Ire Congrès de l asthme* Paris Masson 1932 495—534
4 FRUGONI C SERAFINI U *2e Co g ès Int de l asthme* Mont Dore 1950 454
5 CASTEX, M *2e Cong es Int de l asthme* Mont Dore 1950 391
6 DUCHAINE J *2e Congres I t de l asthme* Mont Dore *1950 9?*
7 BIOZZI G HALPERN B N BENACERROF B *Acta allerg Suppl III* 1953 184
8 SPUŽIĆ V BATA A Cvetojević M 1955 (in press)
9 BEZANÇON F *L asthme* Paris Masson 1932 34
10 FRUGONI C MELLI G *L asthme* Paris Masson 1932 495—534
11 DANIOPOLU D *L asthme* Paris Masson 1932 535—556
12 JACQUELIN A *L asthme* Paris Masson 1932 18 —210
13 BRAY C *L asthme* Paris Masson 1932 401—408
14 MARANON G *L asthme* Paris Masson 193. 435—464
15 DJURIČIĆ I SPOUJITCH Vl *Arhiv a hig Rada Vol 4* 1954 325—348
16 PARROT I *Presse Méd* 1952
17 FRUGONI C SERAFINI U *L asthme* Paris 1950 456
18 COOPE I *2e Co g ès Int de l asthm* Mont Dore 1950 422
19 SPUŽIĆ V *Srp a hiv 4* 1947 229—245
20 SPUŽIĆ V DANILOVIĆ V *Srp Arhiv 7—8* 1950 488—495
21 SPOUJITCH VL DANILOVIĆ V *Co gres I t de l asthme* Mont Dore 1950 493—500
22 BRUUN E *Acta allerg Vol III suppl 1* 1950 239
23 PASTEUR VALLERY RADOT MAURIC G HUGO A Desensib lisation ou accoutumance *Presse Méd 30* 14 avril 1934 *P esse méd* 1954 7 juillet 1934
24 DANILOVIC V VERBIĆ N *Srp Arhl 11* 1952 1008
25 DANILOVIC V BOGDANOVIĆ M 1954 (in p ess)
26 FINDENSEIN D R G *Acta allerg* 1953 162—164
27 PASTEUR VALLERY RADOT *Comment tra ter l asthme de l adulte* Paris Flammarion, 1953
28 SPUŽIĆ V BOŽOVIĆ, B DANILOVIĆ V *Zbo nik Rad San* XX Inst za fiziol rada knj 1 195 43
29 SPUŽIĆ V PUJEVIĆ S PAVLOVIĆ V *Zbornik Rad San knj 2* Bgd 1954 107—114
30 SPUŽIĆ V SRBINOVI Lj *Zbor ik Rad San knj 2* 1954 93—100
31 SPUŽI V DANILOVIĆ V PUJEVIĆ S *Zbo nik Rad San k j 2* 1954 27—35
32 SPUŽIĆ V *Med P egled* 1938 *12*
33 SPUŽIĆ V *S p Arhiv 4* 1948 301—7

34 Blaumoutier, P *2e Congres Int de l asthme* Mont Dore 1950 346—355
35 Pasteur Vallery Radot Blaumoutier *Presse Therm et clim II* 1932
36 Turban K. Spengler *Annalen des Schw Balneol Ges* 1906
37 Danilovi V Verbić N *Congrès Int d Hydroclim et de Thalassother* Opatija 8—13 May 1954 40—42
38 Spoujitch V Pujević S *Congres Int d Hydroclim et de Thalassother* Opatija 8—13 May 1954 12—13
39 Villaret M Bezançon J *L asthme* Paris Masson 1932 306
40 Santenoise D *2e Congr Int de l asthme* Mont Dore 1950 32
41 Haibe *L asthme* Paris Masson 1932 131—146
42 Harley D *The Practitioner* 1953 170 333
43 Bozovi B *Srp Arhiv* 1948 11—12
44 Jimenez Diaz *2e Congrès Int de l asthme* Mont Dore 1950 419
45 Dowall *L asthme* Paris Masson 1932 392—400
46 Rackemann F *2e Congres Int de l asthme* Mont Dore 1950
47 Dowall *Acta allerg Suppl III* 1953 7—12
48 Stern P *Med Pregled 3* 1954 207
49 Parrot J L Laborde C *Presse Méd 63* 1953 1267
50 Danielopolu *L asthme* Paris Masson 1932 535—556
51 Santenoise D *2e Congrès Int de l asthme* Mont Dore 1950 32—66
52 Dowall *L asthme* Paris Masson 1932 392—400
53 Serafini Fabiani De Santis *2e Congres Int de l asthme* Mont Dore 1950 451
54 Pasteur Vallery Radot *Comment traiter l asthme de l adulte* Paris Flammarion 1953
55 Spužić V Pujević S *Internisticka nedelja* Med knjiga Bgd 1953 6
56 Frugoni C Serafini U *Acta allerg III Suppl I* 1950 214
57 Pasteur Vallery Radot et al *Bull des Hôp* 1952
58 Danilović V Gligorova N *Srp Archiv* 1954 12
59 Quarles van Ufford *Acta Allerg Suppl III* 1953
60 Storm van Leeuwen *L asthme* Paris Masson 1932
61 Vuletic V *2e Congres Int de l'asthme* Mont Dore 1950
62 Pasteur Vallery Radot Blaumoutier *L asthme* 1950
63 Spužić V Jankovic S *Srp arhiv* 1931 2
64 Hansen K *Allergie* Leipzig George Thieme 1940
65 Danilović V Nikolic, M Devecerski M (in press)
66 Jimenez Diaz *L asthme* 1950
67 Leriche R Fontaine R *L asthme* 1950 381
68 Jakovljević V Putnik, M *Hirugija neurovegetativnog sistema* Novi Sad 1948

PULMONARY MYCOSIS WITH AND WITHOUT ASTHMA

by

P J VAN DER WERFF

A short survey will be given of 8 patients with mold growth in the respiratory tract and one case report is presented more in detail They illustrate certain aspects of occurrence and significance of bronchomycosis in relation to bronchial asthma and in connection with the therapy especially in this respect the antibiotics

It is conceivable that a o the allergic skinreaction immediate type may prove to be of value to the diagnostician in distinguishing between genuine bronchial asthma secondary to bronchomycosis and the non allergic asthmalike wheezing symptoms such as in cases of tuberculosis pseudotuberculosis by chronic pneumonomycosis malignant tumors etc

1) As some of you who were present at the Round Table Meeting two years ago here in Utrecht perhaps will remember I told you the story of a patient who in his youth worked on a cucumberfarm

He had a bronchomycosis infiltrative and fibrotic changes and cavities in the right upper lung a gradual development of allergy to the responsible Aspergillus species viz Amstelodami (Mangin) Thom et Church Potassium iodide and creosote in moderate dosage appeared to be of no avail

The treatment with intravenous Neosalvarsan had yielded excellent result in clearing the mycotic infection his chronic asthmatic and bronchitic complaints discontinued

2) The second case was a farmer no known allergies in family whose first attack of asthma and bronchitis symptoms simultaneously occurred while harvesting rye [1]

Together with a pulmonary infection with Staphylococcus aureus he had a mycotic pneumonitis giving rise to asthmatic attacks as secondary manifestation caused by an allergy to a yeast—classified as a new species of the genus Trichosporon now called Tr Behrendii Lodder et van Rij (fig 1)

The administration of Penicillin as an antibiotic against the bacteria made the patient worse as it was accompanied by an aggravation of symptoms

Rapidly his condition showed definite improvement on potassium iodide creosote and intravenous Neosalvarsan

[1] These two patients were discussed in *Ann Allergy 11* 567 1953

In the University Clinic for Internal Medicine Leyden (Head Prof Dr J Mulder) we saw during the last 4 years still more patients with mycotic infections involving the bronchi or areas of lung parenchyma but these 4 cases did not show an allergic sensitization to the fungi chronically present in the respiratory tract

3) A farmer with chronic pneumonitis especially in the right lung The sputum culture gave many colonies of Aspergillus fumigatus

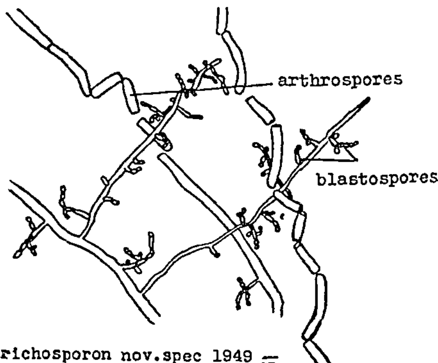


Fig 1

Fresenius Bacteriological findings were inadequate to the clinical manifestations He improved with intravenous Neosalvarsan

4) An agriculturist s wife with a large cavity in left upper lung with growth of an abnormal variety of the species Aspergillus fumigatus In the first stage this was a silent case but later on recurrent hemoptesis established itself Operation was indicated at that time

5) A housewife being in poor general condition got a tonsillar fungus infection followed by miliary dissemination with Candida albicans (Robin) Berkhout after a high dosage cure with Chloromycetin She died

5a) An administrator got a tonsillar fungus infection too in the same way He improved with local application of Neosalvarsan glycerin

6) A gardener with indurative pneumonia His sputum contained large amounts of Aspergillus fumigatus and of the new spec Trichosporon Behrendii With intravenous administration of Neosalvarsan beneficial results were gained quickly

Later on in my Amsterdam clinic we had two clear examples of secondary thrush of the bronchi causing characteristic allergic symptoms in one of them These two patients were sent to Prof Mulder Leyden for further analysis

7) A farmer with chronic *asthmatoid* bronchitic manifestations hemoptesis gradual aggravation of his complaints of coughing dyspnoea tightness in his chest and loss of weight He had a carcinoma solidum of the right main bronchus with an enormous thrush due to Candida albicans His allergic skintests and provocative inhalation tests were all negative

8) A stock farmer with positive allergic family history who since 2 years had a chronic cough since about 1 year rhinitis vasomotoria and asthma bronchiale was hospitalized in very poor general condition He had carcinoma cardiae ventriculi with metastases in both lungs the latter secondary infected by Trichosporon cutaneum (de Beurmann Gougerot et Vaucher) Ota and Aspergillus nidulans (Eidam) Winter and moreover T B Mycobacteria bovine variety were found in pleural exudation at both sides After allergic investigations and treatment with potassium iodide and creosote the allergic manifestations discontinued together with a nearly complete disappearance of the fungi So we felt justified in concluding that the chronic presence of the fungi started the allergic symptoms of the whole respiratory tract

9) Only one patient I would like to present to you today more in detail because this case illustrates certain aspects of the clinical findings diagnosis and treatment He is a baker s son with positive allergy in family history who had recurrent and increasing asthmatic bronchitis since his childhood When he was first seen by us he was 12 years old He had allergic skinreactions markedly strong positive for eggs chocolate milk fish wheat and rye flour several yeasts and quite a lot of molds among others those which are characteristic as defilements for flour (Rhizopus arrhizus Fischer Rhizopus nigricans Ehrenberg Mucor racemosus Fresenius Mucor spinosus v Tieghem Thamnidium elegans Link) Treatment with anti allergic diet and desensitization against the inhalants gave a rapid improvement After 3 months he had no complaints any more After reaching a rather high dosage the desensibilization injection-cure was gradually discontinued 6 months afterwards

The patient showed a perfect health during nearly 3 years also while working in the bakeryshop of his father He came back with complaints of very heavy tickle coughing spells now and then expectoration of abundant amounts of milky whitish sputum lancinating pains in his chest especially at the right side no genuine asthmatic attacks no fever at all these complaints were lasting about 4 months As was told to us all troubles had failed to respond to any treatment during that time When staying out of the bakery he could not find any improvement of his complaints His recent history revealed that these troubles started when during two weeks in summertime he helped his uncle a farmer in harvesting hay Intracutaneous and inhalation provocative allergen tests were negative Antireagins to yeasts and molds could be demon strated The corrected sedimentation rate was 36 mm one hour 80 mm two hours other bloodfindings disclosed no pathologic changes sputum contained moderate amounts of eosinophiles and Haemophili influenzae a few pneumococci of high type and a considerable amount of mycelium threads falling to pieces namely in arthrospores and with blastospores mycological examination disclosed for the third time in a few years the new spec Trichosporon Behrendii The chest x rays November 9th 1953 (fig 2 and 3) gave especially in the right lower chest a paracardial intensively marked picture with an increased density lying in a lung segment at the front side After treatment with potassium iodide and creosote his condition improved quickly together with the findings in his sputum After 4 weeks the check up of the sputum revealed no yeast substances any more still a few pneumococci but more haemo phili than before

The chest x rays made at about the same time December 8th 1953 (fig 4) showed significant decreasing of the pneumonic infiltration The chest x rays of March 17th 1954 gave only slight fibrotic changes in the right lower lung lobe

Referring to the bacterial infection learned by similar observation (case no 2) and by the 2 cases of Leyden I did not give any antibiotics during the first time of the antimycotic cure for fear of the possibility to activate indirectly the fungal infection Afterwards antibacterial therapy appeared to be unnecessary since he had no symptoms and no sputum any more

Comment

Apparently being not as rare as mostly hitherto considered this paper was presented first in order to demonstrate *the possibility of active cases of bronchomycosis* as one of the many causal factors of asthmatic or asthmatoid symptoms and in cases of subacute or chronic bronchitis bronchopneumonia indurative pneumonia or chronic pneumonitis

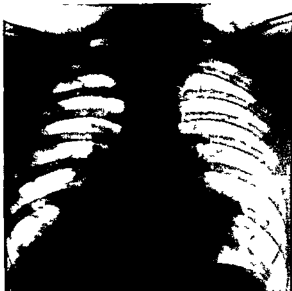


Fig ~
X ray 9 XI 1953



F g 3
X ray 9 XI 1953

Literature

BARNARD J H *Med J & Rec* 139 534 1934
BRASS H E *J A M A 143* 1041 1950
BOCCIA BROCQ—ROUSSEAU et al ORIE Thesis 1946
BRONKHORST W *Ned Tijdschr v Geneesk 86* 605 1942
CAMPBELL J M *Brit M J 2* 1143 1932
CARTER R A *Radiology 26* 551 1936
CASTELLANI A *J Trop Med 24* 149 1921 *28* 257 1925
— *Arch Dermat Syphil 16* 383 571 714 1927 *17* 61 1928
COUNCIL PHARM CHEM *J A M A 145* 1267 1951
DESCLIN L GEPT W DESNEUX DR J *Act Clin Belg 5* 90 1950
DODGE C W *Medical Mycology* St Louis 1935
DUTTON L O *Ann Allerg 5* 439 1947 *7* 585 1949
GALBREATH W R WEISS CH *Arch Int Med 42* 500 1928
HAMIL B M *Am J Dis Child 79* 233 1950
HAUPT E *Klin Wochenschr* 570 1949
HELVE O et al *Act Path Microbiol Scand ?8* 44 1951
HOFFMEISTER W *Zeitschr Klin Med 147* 493 1951
— *Artz Wochenschr 47* 1105 1951
— *Klin Wochenschr 301 1951*
HOLLSTROM E *Acta Med Scand Suppl 144* 1943
JONES B H *Brit Med J 1* 368 1934
KEENEY E L *Ann Int Med 33* 418 1950
KLIENEBERGER C *Deutsch Arch Klin Med 174* 143 1933
KLIGMAN A M LAMATER E D DE *Annual Rev of Microbiology 4* 283 1950
KOTKIS A J et al *Arch Int Med 38* 217 1926
KRAAN J K ORIE N G M *Ned Tydschr v Gen 93* 530 1949
LOHMAN A J M *Ned Tydschr v Gen 85* 3240 1941
— *Ned Tydschr v Gen 88* 661 1944
LOONEY I M STEIN T *New Engl J M 242* 77 1950
MARETT P J *Brit Med J 1* 808 1929
NICAUD P *Presse Méd 2* 1521 1926
ORIE N G M Thesis 1946 Utrecht Holland
— *Ned Tydschr v Gen 91* 3535 1947
— *Ned Tydschr v Gen 91* 3576 1947
PEUTZ J L A *Ned Tydschr v Gen 76* 446 1932
POPOFF T W Ref *Berliner Klin Wochenschr* 601 1887
RÉNON L *Étude sur l Aspergillose* etc Paris 1897
SARTORY A (et al) *Champignons parasites* etc Paris 19.1
— *Compt rend Soc Biol 89* 179 1923
— *Comp rend Acad d Sciences Paris 216* 4?6 1943
SMITH D TH *J A M A 141* 1223 1949
SHREWSBURY J *Quarterly J M 5* 375 1936
STEINFIELD E *J A M A 8?* 83 1924
SUTHERLAND C G *Med Clin cs North America 8* 1273 1925
TERSÁNCKY J *Oesterre ch Med Wochensch 9* 259 1848
VIRCHOW R *Vi chow s Archiv 9* 557 1856
WERFF P J VAN DER *Ann Alle g 11* 567 1953
WOODS I W *J A M A 145* .07 1951
ZIMMERMANN L E *Arch of Path 50* 591 1950

ADDITIONAL LECTURES

ALLERGOLOGY AS A BASAL SCIENCE AND AS AN INDEPENDENT SPECIALISM *

by

H A E VAN DISHOECK

In modern medicine the doctrine and study of allergy has won for itself a recognized position as a basal science in many different specialisms as an auxiliary science in the performance of special techniques and also as an independent specialism with respect to a certain group of affections This result has been obtained thanks to a small group of enthusiastic experimenters and clinicists who however had to overcome an unusually strong resistance

The first observations concerning allergic diseases date back to remote antiquity But it was not until 1873 that Blackley discovered the cutaneous reaction to pollen in hay fever patients With this, the connection was demonstrated ad oculos for the first time between a seemingly innocuous substance and human allergy Blackley thereby became the first clinical allergist

His contemporaries failed to realize the fundamental importance of this discovery On the contrary under the influence of Pasteur s and Koch s discoveries it was thought that hay fever too was probably a bacterial affection Here an analogy with our own times at once suggests itself under the influence of psychosomatic medicine many physicians tend to regard asthma and even hay fever as psychogenic in origin Such one sided exaggerations are understandible because both infection and mental factors play a considerable part in allergic affections

Not until the development of the immunity theory by E von Behring and, more particularly the discovery of anaphylaxia by Richet—now fifty years ago—did the doctrine of specific hypersensitiveness penetrate to the clinic Richet had demonstrated that an animal can be sensitized by injection of a relatively harmless substance and that re injection of a small quantity of the same substance may be followed by severe phenomena such as asthma This soon caused the medical profession —encouraged moreover by Dunbar s writings—to set aside any lingering doubt concerning the causative action of pollen in hay fever Blackley and Dunbar in fact have laid the foundation of allergology as an independent specialism

Specialization also in the case of allergy is the unavoidable result of the ever progressing widening and deepening of our knowledge That

* Lecture held at the Opening Ceremony Prof VAN DISHOECK, president of the Dutch Society of Allergy was president of the Executive Committee

which fifty years ago was an isolated observation and a group of diseases against which physicians were powerless has become a science and technique which can hardly be mastered any longer by a single individual The narrowing down of one s interests that may be the consequence of unduly far reaching specialization is often—and quite rightly—railed at but we are equally justified in pointing with gratitude to scientific discoveries which humanity owes to this same specialization The true specialist is he who concentrates on some part of medical science but who—just as consciously—keeps an open mind and a broad vision for those facets in other specialisms which are necessary for the understanding and the growth of his own subject This entails the need for contact with other specialists and team work

The modern hospital with its many departments and laboratories is the realization of this growth of specialization and integration Here organologists have their own rounded off field of activity Characteristic of these specialists is their engrossment in the basal sciences and their great need of assistance from other specialisms Especially the rhinologist the lung specialist and the dermatologist have been led to study allergy Some have acquired the necessary knowledge by themselves others had recourse to the assistance of a professional allergist In this way allergology has gone through a development similar to that of haematology endocrinology and bacteriology

In most cases these specialisms although not bound to one particular organ nevertheless have some separate disease on which they focus their attention One might even say that a specialism may owe its existence to some particular disease which is both frequent and difficult to cure Such for instance is the case with rheumatology and the same applies to allergology If asthma had been a rare disease there would have been no demand for an independent allergist In that case allergology would have remained like bacteriology a basal science in each specialism Asthma therefore caused allergology to grow into an independent specialism

In common with bacteriology allergology largely owes its scientific development to the laboratory In the beginning both served in the clinic as basal sciences and as auxiliary sciences Bacteriology however is the clinicist s basal science to such a degree that the bacteriological specialist has his place exclusively in the laboratory whereas the allergic specialist has found his place at the sickbed and even here and there already in a department of his own The time when this was otherwise is still fairly recent and even now allergology s struggle for its rightful place has not been brought to a succesful issue everywhere It is doubtful whether any other specialism has encountered greater difficulty in the fight for its independence

This resistance against allergology is not merely the usual reaction against everything that is new and stems from the laboratory Quite rightly novel theories of this kind must first prove their practical value before they can expect to find general acceptance Thus allergology had to prove that specific sensitization plays an important part in a disease like asthma that the causative allergen can be traced and that elimination of this allergen or desensitization can cure the patient This assignment amounts to the demonstration that the anaphylactic experiment is applicable to the allergic attacks The question now is whether allergology has been found wanting in the performance of this task

There is one disease in which this connection is as plain as a pikestaff, and which in fact may serve as an example of a purely allergic affection This is hay fever For both the nasal symptoms and the asthmatic trouble which constitute the hay fever syndrome are known to be caused by a well known allergen grass-pollen In the absence of this allergen—as in wintertime—the morbid symptoms disappear and the patient is a normal person again Exposure to the allergen—also in wintertime—will at once cause the recurrence of the symptoms No wonder therefore that the doctrine of allergy has found its warmest supporters among rhinologists One example of this is the Dutch school of Benjamins Directly in line with hay fever we may place occupational allergies, as in bakers leather workers persons charged with the care of animals hyper sensitiveness to dust in nurses and to cosmetic powder in hairdressers etc In these affections too the allergen is unmistakably recognizable as the morbid agent Again some skin affections and nutritional disorders may be attributed to the action of well known allergens

In all these patients the connection between the disease and a specific allergen is undeniable, in fact the correspondence to the anaphylactic experiment is practically perfect It is not surprising therefore that it was considered justifiable to generalize this observation and that such causative allergens were searched for also in other patients suffering from asthma and other allergic diseases Now the skin tests were expected to do their bit in tracking down the unknown allergen That after all was the necessary condition either for the elimination of the allergen from the patient s milieu or for desensitizing the patient to the allergen

In this way the expectation was aroused that by investigating specific sensitizations by means of skin testing the problem of asthma and vasomotor rhinitis might to a large extent be solved

Disillusions were bound to be frequent for such a success could be completely achieved only in a limited number of patients For a much

and who failed to react to the introduction of pollen into the nose—in about one per cent of cases a positive skin reaction to pollen Nevertheless some of them had a relatively low dermal threshold and in correspondence therewith a high reagin content of the blood This proves that there must be other factors apart from the presence of reagins if an allergy is to be rendered manifest

Piness and Miller found that among the allergic patients that reacted to pollen only half had any hay fever trouble The other half therefore must be classed as cases of either latent allergy or para allergy

In common with Roux we found that bakers who were hypersensitive to flour showed such para allergic positive pollen reactions in about half of the cases while there was only an isolated case of typical hay fever during the season This is a considerably higher incidence than that of positive pollen reactions in other allergies One is naturally inclined to explain this curious association of flour and pollen hypersensitivity by assuming a chemical similarity between the allergens This is known to exist between the grasses mutually but although the different brands of flour also belong to the gramminaceous plants they differ from the grasses in an allergic respect For this reason we only rarely find the contrary case namely a positive reaction to flour among hay fever patients

All the same we are inclined to assume that this association of flour and pollen allergy is not merely accidental and that their kinship becomes manifest in the form of a predisposing factor That is to say that the patient who is hypersensitive to flour is disposed to be also hypersensitive to pollen and conversely This disposition however will not become manifest unless and until the exposure to the allergen in question is sufficient Now the exposure to pollen of the man who works with flour is normally present hence the high percentage of manifestly positive reactions The exposure of the hay fever patient to flour on the contrary is usually extremely slight hence the small number of manifest reactions But when a hay fever sufferer becomes a baker he should according to this theory very soon develop a sensitivity to flour Now this is in fact the case Thus out of some hundreds of bakers we have never found a positive pollen reaction without a simultaneous positive flour reaction

Next to the changeability of the results of the skin reactions the equally haphazard occurrence of the attacks is also a cause of a great deal of misconception concerning allergy In contrast to the laboratory animal which can be made anaphylactic at any time and invariably reacts with an attack to a given amount of allergen the human allergic constitution is to a large extent determined hereditarily and the occurrence of an attack is in a high degree independent of the allergic dosage

Opponents of allergology are able to report cases of patients with positive skin reactions to a certain allergen but in whom exposure to this allergen sometimes produces a reaction and sometimes not at all

Constitution disposition and exposure are the three pillars that support our understanding of the occurrence of attacks The allergic constitution causes children of allergic parents to get allergic affections at an earlier age and in greater numbers The disposition determines whether at a given constitution and exposure to allergen an attack will, or will not occur This disposition comprises somatic psychic and local factors which together determine the tolerance threshold of the autonomous nervous system With respect to the somatic factors one should think particularly of hormones and of infection and with respect to the local factors first and foremost of reflex hypersensitivity

Exposure to the allergen is the third condition both for the genesis of an allergic affection and for the occurrence of attacks This factor is no less important than constitution and disposition The occupational allergies have taught us that any group of the population may at any time be sensitized up to a high incidence by an intensive exposure to a potent allergen Thus bakers in small badly ventilated bakeries proved to be sensitized to as high as 40 per cent and in the large well ventilated ones to 25 per cent The percentage of sensitized workers was found to increase parallel with the number of years of service so that we may well ask ourselves whether given sufficiently long and intensive exposure every person might not be susceptible to sensitization In that case a positive heriditary taint could only become manifest through an earlier occurrence of the allergic disease

The doctrine of specific sensitization is now once again finding its opponents—this time in the ranks of the psychosomatic therapists They deny the importance of specific sensitization on the ground of the desultoriness of the skin reactions and of the allergen as a morbific agent As against this they hold that the cause of allergic diseases must be sought in psychic conflict situations They point to the neurotic disposition of asthma patients to their suggestibility during the occurrence of and the recovery from attacks and to the results obtained by their treatment They deny therefore that in man anaphylactic processes play an important part

No allergist would ever deny the great importance of the psyche in a human allergic disposition Conditioned reflexes and associations are powerful factors in the occurrence of these diseases The familiar examples described by Osler and Morell Mackenzie such as asthma on looking at artificial flowers and hay fever on looking at a painting are readily supplemented by any allergist from his own experience The

same mechanism is equally well known with regard to seasickness and gastro intestinal disorders

But it would be going too far to deny the unmistakably close correspondence between the animal experiment and human allergy And it would definitely be going too far to attribute neurotic tendencies to entire groups of the population such as hay fever patients bakers and others who might be exposed to allergens

The implication of such a theory would be that 40 per cent of people are neurotic since—according to Vaughan—this is the percentage showing allergic symptoms at some time of their life

As against this too little attention has been given to somato psychics, that is the mental digestion of the fact of being bodily ill Is it surprising that an asthmatic child seeks help for his distress in his feelings of suffocation with his mother and that he may develop an ambivalent attachment to her? Surely adaptation to the presence of disease is quite as difficult in the case of asthma as in deafness, infantile paralysis or disequilibrium Those suffering from acquired diseases of this kind show considerable resemblance with asthma patients but nobody would wish to assert that they had a neurotic constitution before they fell ill Neither can it be maintained that an excessively large number of allergic affections is found among evidently neurotic patients

When we reflect upon the controversies which I have discussed we find ourselves faced with the task of giving a reasonable evaluation of many different factors and a justifiable description of their interplay Skin reactions have their value but the allergist should beware of arousing unfulfillable expectations In the pathogenesis of allergic diseases a large number of—partly unknown—factors play a part There are unmistakably somatic factors such as allergens hormones and infections but there are equally unmistakable psychic factors such as existing conflict situations conditioned reflexes and the mental digestion of bodily distress

We cannot help therefore being forced to look upon the allergic syndrome not as either somatic or psychic but as both somatic and psychic This line of thought will come easier to the thinker trained in the philosophy of Hegel than for him who prefers to adhere to the Kantian laws

For the understanding and the treatment of such complex diseases therefore the allergist needs to possess a great flexibility of thought No longer can he afford to be the skin scratcher of former days he will have to master the vast field of specialized allergological knowledge This however is not enough for he must also have a fully adequate knowledge of internal medicine Only in this way is it possible to obviate diagnostic mistakes And even then he is not completely equipped for his work for he will also have to study his patient s psychic condition

That the awareness of these de ıderata ıs not new or foreign to us will be clear to anyone who has made himself acquainted with the program of the adresses for the next three days During these three days both the asthma specialists and representatives of other branches of medicine will give proof of the measure in which the doctrine of allergology in all its facets and as an independent specialism, a basal science and an auxiliary science is a living part of their professional study and deep concern

But apart from knowledge great zeal and high accuracy the allergist must have a warm human heart He must be able to cope with disappointments and to impart courage and consolation over and over again, to these patients who need his moral sustenance more than others

ON THE HISTORY OF BRONCHIAL ASTHMA *

by

TH H SCHLICHTING

An attack of bronchial asthma makes an enormous impression and one cannot wonder that it has been mentioned already among the first medical accounts In fact bronchial asthma is mentioned in the Hippocratic collection sometime between 500 and 300 C

The description is rather accurate since the expiratory dyspnoea has been noticed and laid down in script

Now a modern physician expects that the Greeks would make haste to distinguish between this and cardial asthma bronchitis and similar affections But this was not the case Their idea of the composition and structure of the body was so extremely simple that they could not conceive a great number of different diseases to be possible In their therapeutic measures they took their clue from the general condition of the body and they did not care much about localization and specificity This was the prevailing view and this state of affairs remained unshaken as long as the Greek philosophy of nature and notably that of Aristoteles did prevail

I have named the word specificity This is a rather modern idea its history may be said to begin with Paracelsus it was unknown with the Greeks

Celsus in the first century of our aera, says There is a disease situated in the regions of the throat which causes difficulty of breathing When this disease is not too strong and thus not causes suffocation it is called dyspnoea when this disease is stronger and also causes noises and cough it is called asthma when it is still stronger so that the patient can only breath with the neck extended it is called orthopnoea

Thus all these affections are considered as one disease in different grades of strength

The first full length description of bronchial asthma has been written by Aretaeus of Cappadocia probably in the first half of the second century

As to the causes of illness the Greeks thought that they were either a shortage or an excess or a wrong quality of one of the four liquids the four humours that is of the body and they directed their therapy to the re-establishing of the harmony between these four blood phlegm white gall and black gall

You can express their pathology in terms of these humours but

* Lecture held at the Opening Ceremony

you can do the same in terms of the four qualities viz heat cold moisture and dryness because each humour represents a mixture of two qualities and then you get four possible mixtures As a matter of fact this theory was not so bad as it seems to us they were able really to adapt their therapy to the different pathological states of the body But there was another theory preconized by Galen that was far worse and in reality fantastical It is the theory of catarrhs

Galen imagined but not for the first time that gases rose from the lower parts of the body unto the brain which was the cooler part there the gases were condensated and from there flowed down and caused catarrhs—catarrhein means flowing down—of the nose the eyes the lungs etc

The nature of bronchial asthma could be known only after the theory of catarrhs was discarded after the destruction of the theory of humours and not before same idea of specificity had been conceived and constructed

The modern idea of specificity was in medicine unknown during the Middle Ages In the footsteps of the Ancients people said that man was more real than a man or that the species man was more real than the individual man This kind of viewing nature did not allow them to appreciate individual differences i e did not allow them to conceive specificity in our modern sense It comes to the fore for the first time in the writings of Paracelsus and becomes strong in the following times

The theory of catarrhs was not so very popular in the Middle Ages To be certain of this I have consulted an edition of Avicenna who was from the 13th century in medieval eyes the greatest master of medicine an edition annotated by Jacques Despars a Belgian from Doornik who was a professor at the Sorbonne about 1450 and whose annotations were six times as voluminous as the proper text of Avicenna This professor knew all about medieval medicine—he was besides a great benefactor of his University—and he does not mention catarrhs in his writings about asthma The catarrhal theory was revivified in the Renascence as when people had an exaggerated reverence for Galen Jacques Despars treats asthmatic conditions in the same way as he treats other diseases that are caused by superfluous humours

So this is the official theory But you never know In 1552 Geronimo Cardano was asked to cure Archbishop John Hamilton of Edinburgh This bishop was I regret to say overworked aggressive and gluttonous Cardano prescribed small meals ten hours sleep riding on horseback cold showers nose drops with elaterium (cucumis silvestris) a bed of unspun silk a linen not a leathern pillow filled with straw So he knew if I may say so allergy and he knew the role of the nasal mucosa He cured the archbishop

Practice it is clear is richer than theory Clinical theory indeed did not grow in the 16th century which was the century of anatomy The 17th was the century of physiology But the findings of anatomists and physiologists had only few clinical consequences This is because there is a kind of historical law which says that a clinical theory does not disappear as soon as its fundaments are destructed but only when another theory is able to take its place Thus the clinical theory of Galen held good while on the one hand its humoral theory was dis believed but at the other hand no plausible theory was available

The first new clinical theory was that of the chemical theory of life but in Paracelsus and Van Helmont it was combined with a strong vitalism Paracelsus as a matter of fact, did not quite disbelieve in the humoral theory but Van Helmont in the first half of the 17th century attacked this theory furiously, and in particular the theory of catarrhs He showed with many arguments and a few observations that this theory is impossible and absurd Also he gave same clinical histories that are very rich in content

1) A mayor of a big city falls on the head and the shoulders he gets unconscious he awakes and he feels himself very well during the next eight months After these months he has some attacks of asthma In the night he is sleepless and disturbed his mouth is dry he has a little fever an enormous micturition and about three stools in the morning the respiration like a thread is cut off and he suffers from a terrible orthopnoea The attack ends with a manifest bronchial secretion After a few days he is completely restored

2) A healthy sportsman 24 years old suffers his first attack when he comes to visit Brussels the attack takes three days He gets home but cannot sleep but in a sitting posture When he lays down he has a beginning of asthma but not a real attack Some days are bad but in the intervening days he walks and goes hunting High places are the worst and so he avoids Brussels

3) A canon has asthma in summertime no asthma in winter When he has asthma he has itchings an enormous white desquamation of the skin and he looks like a leper His mother had the same itchings and his sister too But the latter was healed after the second childbirth

4) A Franciscian monk has the duty of cleaning the house Every time a little dust is raised the monk is nearly suffocated Also he can not carry fried fish and he gets an attack of asthma Also he has certain forebodings of asthma just like the hunting man

5) A hearty and modest citizen is publicly insulted by a magistrate but he dares not answer from fear of utterly ruin So he is silent but

soon after he is visited by asthma which grows in intensity After two years he develops a moderate dropsy and he dies

Thus Van Helmont who calls asthma epilepsy of the lungs describes emotional asthma allergic asthma from dust and food and climate Also he has a theory about the origin of asthma but a vague and wrong one and I shall be silent about it

His writings about asthma date from about 1630

Now in 1628 William Harvey published his celebrated book on the circulation of the blood and out of this discovery came a strong argument against the catarrhal theory because in 1659 Victor Schneider in his big book on catarrhs endeavoured to show that the catarrhal secretion did not come from the brain but from the bloodvessels in the affected spot About 5 years later Niels Stensen the discoverer of the ductus Stenonianus contended that the catarrhal secretion did not flow immediately from the bloodvessels but from the mucous glands which were discovered and described by him Thus the whole fundament of the catarrhal theory was destroyed first by Van Helmont with arguments then by Stensen with facts

Van Helmont was an iatrochemist his school tried to explain physiology through chemistry but another school which rose in the same time tried to explain physiology through mechanics and since mechanics was at the time the best developed science iatromechanics generally met with better success than iatrochemistry And thus we hear at the same time a mechanical explanation of asthma out of the brain of Willis he considered spasm of the bronchioli as the cause of bronchial asthma

This is a very nice idea But the great Sydenham did not like mechanical explanations and in this case he did not deepen the knowledge of asthma

A rather modern account was given by Sir John Floyer in 1698 but in the next century there was no great advance in the knowledge of asthma The reason is I think that experimental science did not flourish in this century people liked deductive science i e explaining all things through one or two simple principles And so asthma is according to one school nothing but enhanced irritability and according to another abnormal incitability and to still another an expression of an excessive nervous activity and so on

The 18th century was the century of rationalism

In the beginning of the 19th century a new school of medical thinking and investigating was founded by some Frenchmen notably Bichat Laennec and Corvisart

In the previous centuries it had been proven and foremost in the great work of Morgagni that clinical diagnosis most often did not

coincide with post mortem findings The above named Frenchmen thought that the reason of this clash between clinical diagnoses and post mortem findings was in that during life anatomical diagnoses should have been made whereas in reality clinical i e non anatomical diagnoses were made They were not contented with a clinical diagnosis v g chronic pain in the belly with stranguria but they tried to make anatomical diagnoses during life they developed percussion and aus cultation Laennec described for the first time many diseases of the lungs and also of the liver This is a well known fact in medical history but at the other hand their whole way of thinking tended to the as sumption that anatomical diagnoses are the only real ones So we find in the 19th century many more or less anatomical concepts of bronchial asthma

Of course the outstanding theory already more than a century old was a neurological one And this theory crystallized into the widely accepted thesis that bronchial asthma was caused by a cramp of the small and smallest bronchial muscles It sounded very simple and sufficient and it got a thorough exposition by Biermer the man of pernicious anaemia

Before expounding this theory we have to retain that bronchial asthma was in the first half of the 19th century conclusively separated from cardial asthma or oedema of the lungs from emphysema and many other diseases This kind of clinical science was the great harvest of the anatomical school and thus the site was prepared for the building of an etiological theory of asthma

After many attempts by Longet and other people Paul Best a disciple of Claude Bernard elicited an attack of bronchial asthma by stimulating the vagus nerve the attack consisted in a tonical spasm of the bronchial muscles Further Biermer was satisfied that the prolonged expiration and the sibili had to be explained through the bronchial spasm This spasm caused an acute emphysema of the lungs and this emphysema caused the depression of the diaphragma

But why is expiration more difficult than inspiration although the pression of expiration is stronger than the pression of inspiration? According to Biermer this is because the strong pression of expiration compresses also the bronchioli so that expiration is made more diffi cult and furthermore it is a fact he says that in capillary bronchitis the expiration is not strong enough to extrude the mucus and so gives way to emphysema while all the time inspiration is perfectly possible This fact serves as an explanation of the greater difficulty of expiration

Biermer cannot explain why the attack of asthma ends with catarrhal phenomena In his theory there is no place for secretion But about this I shall have to say a few words later on

Now this theory of Paul Bert and Biermer is to a certain extent a physiological one But there were also anatomical theories of asthma in the 19th century in the second half so called physio pathological theories were en vogue

In this case the anatomical theory of Wintrich was of a later date than the physiological one of Biermer

Wintrich saw the origin of bronchial asthma in a tonical depression of the diaphragma against Biermer he contended that bronchial asthma would have as an effect a relaxation not a depression of the diaphragma in fact in asthma the volume of the thorax is diminished the inter costal spaces are drawn in and it is only natural that the diaphragma should be relaxed So Wintrich drew from the depression of the dia phragm all phenomena of an asthmatic attack His explanation had all the charm of the simple and obvious

These was a third theory which had also a great charm Weber contended that bronchial asthma was due to the swelling of the mucosa he saw an analogon of asthma in the swelling of the nasal mucosa this theory was compatible with the role of the nervous system in asthma because one could explain fluently the swelling of the mucosa by the excitation of the nerve supply of the bloodvessels Weber had no difficulty in explaining the secretions and the catarrhal phenomena in asthma And there were experiments made by a certain Loven who was able to induce hyperaemia of the mucosa by excitation of sensory nerves and so he imitated the originating of reflectory asthma

This theory has been consolidated by many considerations and it has many advantages indeed But like the other theories it suffers from the disadvantage that an enormous and cohering complex of symptoms is explained by one single cause which is in itself of an haphazard nature And one feels on the rebound a little sympathy for ways of explanation such as of Van Helmont who thinks that a whole complex of ponderous physiological factors is disturbed and thus causes bron chial asthma which is in itself of a disturbing nature Perhaps I had better say that the physiology of respiration was still thought to be very simple At the present time after fifty or sixty years the 19th century theories retain not a little of their value but modern theories of patho genesis draw the attention to the reaction of the whole organism to a disturbance This way of viewing disease has been fruitful in neurology mainly it seems through the work of Kurt Goldstein and Von Mona kow I do not know whether it has been fruitful in the case of bronchial asthma

When in the footsteps of Lain Entralgo we call the theory of Wintrich anatomical that of Biermer physiological that of Goldstein biological than the next step in viewing disease may be called anthropological

or psychosomatic This way is opened by the theories of Freud and so bronchial asthma has been viewed as a symbolical disease

Not only specialists but also general practitioners like myself, have seen cases of bronchial asthma which were symbolical expression of internal emotion for the most part I think of indignation and powerless anger This view enriches our knowledge and to a certain extent also our understanding our knowledge because emotional asthma was rather forgotten and was certainly not rightly appreciated it enriches our understanding to a certain extent only because the so-called relation between body and soul has not become clear and diaphanous but only better appreciated and the nature of symbolical expression is better understood It remains that the whole affair is very difficult and certainly not to be expressed only in terms of anatomy and physiology At the other hand the anatomical and physiological problems *have not been superseded by the psychological view but they are not* the sole problems and it becomes very clear that they are *part* of the life problem

But we can safely say that the psychological view has a great therapeutic value because in order to cure a patient it is not necessary to understand his disease in its entire essence In former times medical men have cured many diseases while floating in clouds of ignorance And this state of affairs will remain I think a few years longer Understanding of asthma has grown in the 19th and 20th century the problems have become more difficult became more extended but at the other hand the investigator has got more facts It seems to me however that the constitution of the asthmatic patient has not received enough attention medical science has forgotten constitution and temperament since 1800 It is to be expected that understanding of bronchial asthma will be deepened by the new kind of pathogeny which is the fundament of the theory of stress as laid down by Selye and others but this question is not yet a historical one

Therapy always follows the theory of pathogenesis When asthma was considered as brought about by superfluous humours derivation and purgation were the logical remedies When the cause was plethora bloodletting was the means of healing and as a matter of fact Van *Helmont and Sydenham advocated bloodletting Now extensive blood* letting is practically a kind of hibernation and one should not wonder that many cases are healed in this way In the 19th century the idea of specificity grows enormously and everyone looks for specific remedies the now well known remedies were in the beginning often regarded as being specific With endocrinology a powerful agent has been discovered adrenalin or suprarenin But right through the big stream of reigning theories are the cross currents of emperical knowledge

Strammonium and other such agents are discovered in this way And in the school of so-called nature healing diet water cures and gymnastics are applied

But as the exposition will show you all kinds of therapeutic measures I need not enlarge upon therapy

I may conclude with the expression of the hope that you shall draw both from theoretical and emperical knowledge many old and new means of curing asthmatic patients and I thank you for your gracious attention

THE SOCIAL SIGNIFICANCE OF BRONCHIAL ASTHMA *

by

P MUNTENDAM

Summary

The treatment of the sick, the fight against disease and the social therapy can only be organized consciously and effectually providing the social etiology is known and the social diagnosis has been deter mined in addition to which the social prognosis must be included in the subject of study In former times the organized fight against disease and the social care of the people s health was still insufficiently based on the results of socio medical investigation

History

In antiquity it was especially Hippocrates who attached importance to climatological factors in the genesis of asthma Galenus sought an explanation of asthma from the angle of humoral pathology Maimo nides towards the end of the Middle Ages points to the asthma patient s hypersensitivity to certain substances and this is confirmed in the 18th century by William Cullen Meanwhile as early as the 17th century the hereditary tendency to asthma had been pointed out while the bronchial spasm—which too had already been discovered by that time—was confirmed by the development of 19th century physical diagnostics New concepts allergy and anaphylaxis begin to occupy medical thought while the psychogenic factors and their proximate causative action call for increasingly serious attention

Definition of the concept

The definition of the concept asthma may differ according to the views held with respect to the genesis of the disease The attacks of bronchial constriction constitute the nucleus of all such definitions

Social etiology

In close connexion with the etiology of individual cases we should bear in mind the influence of the patient s milieu causes which either act through physical mechanical chemical or biochemical factors or should be ragarded as mental and/or social milieu influences Among the first group the patient s housing the factory or workshop the climate his

Lecture held at the Opening Ceremony Dr P Muntendam professor in the University of Leyden (Holland) is Director General of Public Health

diet and further animals plants and micro organisms may play a part The mental milieu is especially determined by the atmosphere prevailing at home and at work the social milieu depends among other things on the patient s economic circumstances

This part of our study includes also genetics It is generally assumed that the heredity of an allergic constitution is irregularly dominant It is this constitution which determines the individual s asthmatic reaction either to a psychic conflict or to the action of an allergen

Social pathology

The significance of the disease for society (social pathology) constitutes its social significance in a restricted sense

Morbidity According to the records of the Centraal Beheer (i e Netherlands Central Administration Office of Social Insurance) the number of cases of asthma per 100 workers in 1937 was 0 10 per cent and in 1953 0 36 per cent This would mean that out of the total population of the Netherlands 36 000 persons were absent from their jobs in 1953 on account of asthma The increase of the number of asthma cases is the more evident when we find that the total number of cases of all diseases was in 1953 only double that of 1937 Further other diseases in which a psychogenic cause may be assumed also increased considerably in the Netherlands after the war so that the rise in the incidence of asthma also points in the direction of the psychic factor in the genesis of the disease

From two different investigations (Orie at Groningen and Groen with the Philips concern Eindhoven) it appears that the total number of asthma patients in the Netherlands is greater than the number of absentee workers Both these investigations show between 1 and 1 5 per cent of the population which would amount to about 100 000 asthma patients in the Netherlands

There exist no clear and reliable data concerning the spread of the disease in this country But what does strike one is the fact that the number of men rejected for military service on account of asthma is invariably and considerably lower in the southern provinces (Limburg N Brabant) than the national average while the north western province (North Holland) is constantly far above the latter average

The investigation in school children held last year showed that morbidity among these children was about equal to that among adults viz ± 1 per cent

It is already clear from the above data that *in the Netherlands asthma is of very great social significance*

According to the data published by Unger showing that 60 per cent of asthma patients are between 20 and 40 years of age this means that in

the Netherlands there are about 60 000 asthma patients in the age classes of productive workers

Course of the disease The *mortality rate* due to asthma is not very high in the Netherlands In 1950 it was (standardized) for men 6 1 per 100 000 inhabitants which is slightly below the asthma mortality in Britain (Williams 7 1 per 100 000 inhabitants in the years 1930 – 1948) For women the death rate was lower viz 4 4 per 100 000 inhabitants The asthma mortality figures however have trebled in the Netherlands since 1920 but closer analysis will be needed to show whether this increase is in accordance with reality Notwithstanding the relatively low mortality physicians examining persons for a life insurance are somewhat hesitant in accepting asthmatic candidates in view of possible complications or other affections based on an allergic constitution

Although the *duration* per case fell from 30 4 days in 1937 to 24 5 days in 1950 the total number of working days missed on account of asthma was nearly trebled Possible explanations of this may be the intensification of psychic factors as morbific cause after the war and the increased employment of older people among the working population

Invalidity The age spread of those in receipt of invalidity benefit on account of asthma from the R V B (i e Netherlands State Insurance Bank) was in 1952 and 1953 as follows

17 – 20 years	2	40 – 50 years	214
20 – 30	69	50 – 60	251
30 – 40	109	60 – 65	103
		65 and older	17

This total of 765 National Insurance annuities amounts to 2 3 per cent of the total invalidity benefits paid out The total amount paid out on account of asthma was *f* 94 546 68 (68 = cents) On January 1 1955 610 of these annuities were still running 79 being terminated due to patients recovery and 76 owing to death

The percentage of invalidity annuities paid to women on account of asthma out of the total amount of annuities paid to women shows a rising curve i e from 0 6 per cent in 1948 and 0 5 per cent in 1951 to 2 2 per cent in 1953 This too may perhaps be explained by the employment of an increasing number of older women and increasing psychic tensions in connexion with the ever rising industrial productivity

Social and economic significance The total amount of sick pay received by asthma patients from the Central Administration Office of Social Insurance was in 1937 just over *f* 20 000 — and in 1950 nearly *f* 181 000 — viz over 1 per cent of the total amount of sickness benefit paid out Out of a National Insurance Fund covering 200 000 insured

persons an average of 74 patients per year were admitted to hospital at a cost of about *f* 30 000 — This would amount to more than 1 million guilders for the total number of persons insured with a sick fund in the Netherlands for the hospitalization of asthma patients alone

With regard to the non insured section of the Dutch population we are unable to assess the socio-economic significance of disease a fact which is to be regretted particularly with respect to married women and housewives

The testing of a person for a given kind of job is a matter of con siderable socio medical significance also in the case of asthma In addition to declaring a person unsuitable for certain trades (e g in dusty surroundings) the test should also be directed positively i e towards such types of work as the asthma patient may safely be en trusted with

Social therapy The fight against any disease is closely bound up with its causes and its consequences for society while the possibilities of exercising influence in both a prophylactic and curative sense should also be known So long as this is not the case it will be better to direct the available financial means towards scientific investigation rather than towards the creation of a large and expensive organization

The knowledge of the causal treatment of asthma justifies next to supporting scientific investigation also the creation of an organization devoted to fighting the disease In this especial attention should also be given to the psycho somatic treatment of asthma (psychotherapeutic group therapy according to Groen) which has been more and more in the centre of interest in the Netherlands during recent years

Before all however the organized fight against asthma should be directed at *the child* By taking heredity into consideration when giving pre marital medical advice in giving dietary advice to expectant mothers and during the breast feeding period and in creating a psychically and hygienically healthy milieu powerful contributions can be made to the success of this fight More especially organized care of infants in arms and babies by the existing consultation bureaux and their arrangements for district visiting as well as medical supervision in the schools will facilitate attention being given to the children s psychic milieu

Most interesting are the results of the treatment in the Heideheuvel Institution at Hilversum There an extremely pure psychic milieu is created for the children the feeling of being ill is completely repelled the therapy including the absence of any special anti allergy diets All the children join in eating everything So far the results are most gratifying The children s non attendance at school is below that of other Hilversum children After 6 months 73 per cent of the children were well 23 per cent moderate but improved and 4 per cent

without improvement To achieve a lasting result it is especially the simultaneous improvement of the family milieu and the social after care that are important if this physical and psychic sanitation is to be per petuated

For the organization of an early and effectual treatment of asthma in children the following are imperative

1) General guidance and education of the population into under standing that asthma is a disease which can be treated in such a way as to ensure for the child a full future life

2) Individual guidance and instruction of the asthma patient s milieu

3) Early recognition of symptoms through consultation bureaux for infants and babies and medical supervision in schools

4) Creation of scientific centres for investigation and therapeutic advice

5) Foundation of therapeutic institutions

6) Organization of after care

With regard to the fight against asthma in adult patients those measures are of particular importance which are directed towards the improvement of the working milieu both in a physical and chemical sense (Safety Act Stonemasons Act) and in a psychic hygienic sense In this connexion great value must be attached to the establishment of industrial medical services and the medical consulting hours in factories which may make a considerable contribution to the relationships among the personnel in the industry In addition the enforcement of the Partially Unfit Workers Act (2 per cent partially unfit compulsory in large concerns) may be of importance for asthma patients

The implementation of the programme here developed demands the concern and the financial co operation of the entire population Ad mittedly the Netherlands Budget since 1951 has included a modest item (for 1956 ca *f* 400 000 —) but both the Government s contribution and those of the general public towards private organizations remain insufficient for the fight against this socially important disease For this reason this opportunity was seized to stress the great significance for both the people and the individual of an efficient and successful fight against asthma

ASTHMA IN A PARISIAN OUT PATIENTS CONSULTATION *

by

B N HALPERN

The asthma problem in Paris is not very different from that in the Netherlands But due to the great difference between climatic conditions in Northern and in Southern France the frequency the causes and the complications of asthma are quite different in Lille and in Nice

Paris is situated in the northern part of France and its climatic conditions are not very different from those in the Netherlands The patients whose cases will be analyzed here come from our out patients consultation of Prof Vallery Radot s clinic in Hospital Broussais Because the number of hospital beds available in the Parisian hospitals since the war is extremely limited it became a necessity to study and treat asthma patients in an out patients consultation which is similar to a physician s office But unquestionnally there is a crying need for institutions for study and treatment of asthma similar to those used in the treatment of tuberculosis Prolonged rest a convenient diet the choice of suitable climatic conditions the psychological role of the nurses and physicians in whom the patient has confidence the feeling that he is in specialized institutions all this will comfort the patient and make the difficult task of the physician easier

Status asthmaticus cannot be treated satisfactorily in any place but in the hospital Fortunately the incidence of patients in status is very low now This leaves a great number of patients who are ambulatory and who can be studied thoroughly and satisfactorily in a well organized out patients consultation At the out patients consultation of Prof Vallery Radot s clinic which is the only one really specialized allergy clinic about 1000 – 1500 patients are seen every year mostly for asthma

It is most important to explain to the patient on his first visit the nature of the disease with which he is affected Hope of a cure should not be withheld Asthma can be cured completely providing that the patient has not developed changes of irreversible type If emphysema has occured then our prognosis must be guarded and the patient should be relieved and the progress of the disease retarded but a complete cure becomes highly problematic We explain to the patient that no immediate miracle will be performed and that satisfactory results can

* Lecture held at the Exposition

only be obtained by full and absolute co operation between the patient and the doctor and that the treatment must be carried out over a long period of time If the patient is unwilling to co operate on this basis it is best for both physician and patient to part company then and there Asthma is a discouraging disease from the viewpoint of the patient and a difficult one from the physician s viewpoint Consequently asthmatics become notorious shoppers (H L Rogers) They very often become unfaithful to their doctor for charlatans who are able to cure asthma by some miraculous magnetic fluids An attempt should made to dis courage this kind of behaviour

Patients treated at the out patients consultation come from two sources

1) Those referred by outside physicians
2) Those who are sent by other patients

1) For the first group of patients a complete report of the findings is sent to the referring physician Often we are sending the necessary allergen extracts to the physician with brief but definite directions for their use The patient is re adressed to me after the first month of treat ment This visit is very important It is similar to the first visit to the garage of your new car after its running in All symptoms are carefully discussed and a further effort is made to determine what produced them It is important to check the reactions to the allergen injections in order to adjust the dosage

The patient is then referred to his general practitioner with new instructions The advantage of this plan is to build up a teamwork between the general practitioner the patient and the specialist Careful and diplomatic coaching by the specialist brings about intelligent co operation on the part of the referring physician

2) The patients who come direct to the clinic are treated in the hospital by some of the assistants under our supervision The essential elements of the examination are

History the initial history is important It is usually taken by the specialist himself after a general examination by one of the senior students We use history forms which are time saving and tend to a more orderly recording of the facts They should not become too mechanical The patients are requested to tell first their troubles and after that they are inquired about the following facts

The age of onset
The frequency and severity of the attacks

The circumstances of the appearance of the attacks at home at work by day at night?

The influence of the season of the climatic conditions

The nature and amount of sputum

The role of infection

Has there ever been an attack brought on by the use of a drug such as aspirin?

The influence of dust or animal dander

Has the patient vasomotor rhinitis?

Is the patient recovering his breath completely once the attack has passed? This gives an idea about the degree of emphysema

The inheritance factors

Other allergic conditions which have preceded or are concommittant with the asthma

If the patient is a woman it is important to know the role of the menses

What are the drugs which provide relief?

Is the patient using sympatho mimetic drugs?

Is the patient taking any treatment between the drugs?

The physical examination The entire respiratory tract is given a thorough examination We know that the upper respiratory ways are mostly participating in the allergic troubles and their physical aspect gives a very definite idea of the state of the bronchial mucosa A good asthmologue should be also a good rhinologist It is therefore very important to note the aspect of the nasal mucous membrane and the state of the sinuses The nose should be examined for

Presence and aspect of discharge

Color of the mucous membrane

a) pallor and edema denote allergy

b) smooth red congestive membrane usually denotes infection

Presence of polypoid degeneration of the turbinates

Any malformation of the sept

Transillumination of the sinus is a very simple procedure and should be routinely done A great deal of informations can be gleaned from this examination

If the sinus do not transilluminate clearly this examination should be completed by x rays study The aspect of the postnasal pharynx is of interest The examination of the chest is of course of the greatest importance The type of the chest should be noted and if there are symptoms in favour of emphysema the diagnosis should be reserved We should regularly measure the difference of the chest circumference in inspiration and in expiration with a tape measure Spirometry is a routine procedure

The auscultation gives an idea of the respiratory type and shows the various rales By the way I am noticing the presence of humid rales on the bases of the lungs, indicating a heart congestion The condition of the heart is of the greatest importance

The presence of an enlarged liver of peripheral edema, cyanosis must be noted Radioscopy and radiography or tomography are routinely applied

The last part of our examination are the skin allergic tests Scratch tests are the usual procedure with exception of house dust moulds and food allergens for which intradermal testing is applied

When the patient has been tested one should keep in mind that severe general reactions may occur and that the physician should always have at his disposal adrenalin and phenergan

The following allergens are usually tested

House dust Endo 1/4000 1/400

Moulds Cladosporium Alternaria Penicillium 1/100 solution

Feathers

Danders cat dog horse cattle, goat hair

Orris root

Cereals

Orchard and timothy grass

Milk egg cereals celeri tomato spinach some meats

The results of the testing should of course be set side by side with the clinical facts

In our country it is possible to find an allergic cause of asthma in 60–70 per cent of the patients whose asthma started before the age of 30 The percentage of positive reactions decreases abruptly when asthma starts after the age of 40–50

TREATMENT

The problem of the treatment should be considered under two different angles treatment of the attack and the basic treatment

a) *Treatment of the attack*

Adrenalin should be used with caution We are convinced that a too extensive use of adrenalin leads progressively to abuse and aggravates the asthma Many of our patients came to a severe state of status asthmaticus by abuse of sympatho mimetic substances What is true for adrenalin is also true for aleudrine

Theophyllin injected by intravenous route can stop a moderate asthma attack We use a solution containing 250 mgm per 10 ml Amino phyllin should be injected slowly It can be repeated twice or three times daily It can be also administered by intramuscular way or rectally

Morphine should never be administered in status asthmaticus Morphine is responsible of many deaths In severe cases of status asthmaticus we are using now either cortrophine or cortisone For ambulatory treatment we use ACTH by intramuscular route while in hospitalized patients intravenous drip is prefered

Blood lettings are sometimes efficient

Pyrethotherapy is sometimes used when hormones are contra indicated

At our out patients consultation we have an *aerosol room* and very often an aerosol treatment is efficient enough to arrest an asthma attack We are using almost exclusively theophyllin

b) *Basic treatment*

The problem is quite simple for those patients who are allergic to a well known allergen The desensitization treatment which is now applied in many thousands of patients gives generally excellent results In Paris 50 per cent of our patients suffering from rhinitis or asthma are treated in this manner We have about 100 per cent of success in pollinosis and near to 90 per cent in dust and moulds allergy

The pharmacotherapy of these patients must be eclectic and cannot be uniform Some of our patients are using hormones since 3–4 years with a satisfactory state We are using either cortisone 50–100 mgm a day or hydrocortisone 30–40 mgm a day or ACTH The usual Na restrictive diet supplemented with Potassium is applied Theophyllin is one of the most valuable drugs in treatment of asthma particularly when given rectally or parenterally Many associations of theophyllin with coffeine ephedrine phenobarbital iodides exist in France and are largely used

Theophylline is also very often used in form of aerosols This kind of administration is used now not only by the specialist and in the hospitals but by almost every practitioner It is harmless and gives very good results not only in acute state but also in maintenance treatment It is interesting to note that the repetition of aerosol treatments can provide a long lasting relief

Antihistaminics are usually efficient in allergic rhinitis In asthma the results are confusing and irregular We have been able to show that antihistaminics and especially phenergan are regularly active in the prophylactic treatment of asthma which is produced by high molecular proteins such as danders feathers animal proteins In asthma produced by small molecular allergens such as dust moulds allergen and even pollen allergen antihistaminics are not very helpful

It is difficult to explain the difference of action in the two groups of patients Antihistaminics are almost completely inactive in infections

and in non proteinic asthma Our bronchoscopic studies indicate that in these cases local or regional spasm produced by irritation by the modified secretions is responsible for the dyspnoea Theophyllin iodides ephedrin and hormones are much more helpful in these cases

Literature

H L ROGERS Office treatment of bronchial asthma in ABRAMSON H A *Treatment of asthma* Baltimore 1951

PROBLEMS AND POSSIBILITIES FOR THE GENERAL PRACTIONER DURING THE TREATMENT OF BRONCHIAL ASTHMA*

by

A H VAN LIDTH DE JEUDE

Summary

I would first briefly mention the general practitioner s difficulties in treating persistent cases of bronchial asthma because of the feeling of disappointment and annoyance on the part of both patient and physician which further jeopardizes any still remaining chances of successful outcome of the treatment I here distinguish between difficult and troublesome cases and I suggest that instead of resigning himself to the fact or the possibility that a disappointed patient may seek help elsewhere—usually with equally unsuccessful result— the doctor should endeavour to find out whether there may not be certain factors in the circumstances of the patient s personal life that may be responsible for the genesis and/or continuance of the affection and which if revealed and consciously realized may open up a new outlook suggesting different therapeutic measures I will now describe three case histories by way of illustration

Case 1 Man aged 49 married with one daughter Has attacks of asthma when at home (week ends) with his wife and child but never when away during the week Was treated in many different ways without lasting success A private conversation revealed that he had been initiated into the facts of life when a boy of 16 by a widow the mother of a school friend He later married but his wife was cool towards him and their sexual life was unsatisfactory After many years of unsuccessful treatment the long confidential talk with the doctor led to a separation from his wife after which the attacks gradually ceased

Case 2 Woman aged 32 Came for treatment in 1953 having had attacks for 7 years Rather unhappy youth Married in Zeeland after 4 years courtship Father in law indifferent mother in law against the marriage Husband also very callous towards her Coitus very painful Patient says I need a lot of love if anybody is kind to me it does more good than a hundred injections Repeated treatment by internists

Lecture held at the Expos tion

where P = force, V = dx/dt = velocity, Po = isometric tension, a and b are constants with the dimensions of a force and a velocity respectively Arranging the equation in this form makes it clear that the force velocity curve is part of a rectangular hyperbola The form $V = (Po - P) b / (P + a)$ may be more evocative, for it shows that the velocity depends on the difference between the actual force acting on the muscle (P) and the maximum force which it could develop (Po)

Not only does Hill s equation fit the experimental force velocity curves of many different types of muscle but also one of its constants (a) can be determined independently from either mechanical or thermal measurements and the two estimates agree reasonably well

It should be noted that since Po appears in it as a constant, Hill's equation can only be applied near the flat top of the tension length curve, i e where the muscle has about its *in situ* length Moreover, since the elastic component has been eliminated by recording isotonically, the equation applies to the contractile component alone

Dynamic Performance with Various Types of Load

In the region of its *in situ* length the mechanical behaviour of the tetanized whole muscle thus appears to be fully determined by the equation

$$V = (Po - P)b/(P + a) - d[f_1(P)]/dt$$

where $x = f_1(P)$ is the equation of the stress strain curve, known experimentally from Figure 4 This makes it possible to predict how the muscle will react when it is confronted by any specified mechanical system

Inserting the appropriate relationship (imposed by the external mechanical conditions) into the above equation, the following cases have been worked out

1 Isometric contraction V = O therefore

$$(Po - P)b/(P + a) = d[f_1(P)]/dt$$

i e the rate of internal shortening of the contractile component = rate of internal lengthening of the elastic component The

solution to this equation describes the way in which isometric tension rises with time It is in good accord with experimental fact (Hill, 1938, Wilkie, 1950)

2 Imposed constant velocity (Levin Wyman lever) V = const (Hill, 1938)

3 Inertia wheel, P = M dV/dt (Hill, 1940)

4 Inertia + constant force F P = F + M dV/dt

This last is the situation which confronts a muscle in the living body The predicted result, which becomes oscillatory under certain conditions, is in good agreement with experimental findings (Wilkie, 1950)

Although it is easy enough to write down these differential equations it is often impossible to solve them algebraically, because they are non linear The result must then be obtained by computational methods or much more simply and quickly, by building an electrical analogue circuit (Wilkie, 1950) The contractile component is imitated by a battery in series with a non linear resistor, the elastic component by a non linear capacitance and the external load by appropriate inductances (= inertias) and batteries (= forces)

Twitch and Tetanus the Active state Curve

The physical state of a muscle is exactly the same during the early part of a twitch and during a tetanus (after all the muscle cannot know after the first stimulus whether or not other stimuli are coming) However, the contracted state or active state does not last very long, and after only one stimulus there is not time for the isometric tension or the isotonic shortening to reach its full (tetanic) value The exact way in which the active state appears and disappears has been extensively studied in recent years for there is abundant evidence that many drugs act by altering the time course of this process

Definition of active state The intensity of the active state at any instant is defined as the isometric tension which the contractile component can develop (or just bear without lengthening) at that instant The tension in the whole muscle follows a much slower time course because of the series elastic component

(1) *The onset of activity* begins very soon after the stimulus The

first change in mechanical properties (at 0) can be detected after 3 m sec (Hill, 1951b), spontaneous tension development after about 12 m sec (Abbott and Ritchie, 1951), and isotonic shortening after about 20 m sec (Hill, 1951a) Since isotonic shortening begins at its full maximum speed, one may conclude that by this time the active state has already reached its full intensity

(2) *The plateau of activity* Activity remains at full intensity for an appreciable time after the stimulus (40 m sec at 0 C, 10 m sec at 20° C) During this period the muscle behaves exactly as though it had been tetanized (Macpherson and Wilkie, 1954) If the effect of the series elastic component is removed by a quick stretch of appropriate amount (Hill, 1949) or by sudden isotonic loading (Wilkie, 1955, unpublished), the muscle can develop, or bear, the full tetanic tension

(3) *The decline of activity* The apparent duration of the plateau varies inversely with the sensitivity of the tension recording apparatus employed Thus if a piezo electric crystal is used in stead of a transducer valve, the first decline from the plateau can be detected at 34 m sec (Ritchie, 1954a) instead of the 40 m sec quoted above The falling phase of the active state curve can be determined without this ambiguity by the method described by Ritchie (1954b) When the rate of change of ten sion in a muscle is zero its elastic component must be at un changing length This occurs at the peak of an isometric twitch, and since the total muscle length and the length of the elastic component are then both unchanging, the contractile element must also then be neither lengthening nor shortening In this situation the tension which it exerts (which is the same as the tension exerted by the whole muscle) must be equal to the in tensity of the active state, according to the definition given above By releasing the muscle at various instants after the stimulus Ritchie obtains a set of twitch like tension records (Figure 7) The peak of each of them must lie on the active state curve, which is thus indicated by the dashed line in Figure 7

The apparatus is arranged as shown in Figure 7 The (un loaded) lever is prevented from moving by the stop and is

attached to the transducer by a slack connexion The amount of slack does not matter so long as it is greater than the amount by which the series elastic component is stretched at the height of contraction—that is about 1 5 mm (see Figure 4)

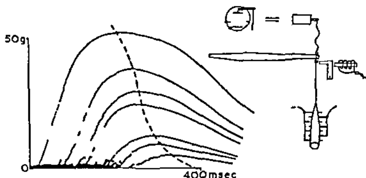


FIG 7 The active-state curve Apparatus and experimental tension time curves The dashed line drawn through their peaks shows the decline in intensity of the active state

When the muscle is stimulated it develops tension isometrically, but this is not recorded When the stop is suddenly removed the series elastic component shortens abruptly (as in Figure 3) and the tension falls to zero However an active contractile component then redevelops tension which is recorded as in Figure 7 The later the release the less tension redevelops

The active state curve is very easily influenced Its falling phase is delayed by adrenaline caffeine (Goffart and Ritchie 1952), nitrate, bromide iodide (Hill and Macpherson 1954), quinine (Lammers and Ritchie, 1955), certain quaternary ammonium salts (Ritchie and Wilkie 1956) also by previous stimulation (Ritchie and Wilkie 1955) decrease in temperature (Macpherson and Wilkie 1954) or increase in hydrostatic pressure (Wilkie 1954 unpublished) These effects are probably all mediated at the surface of the muscle fibres (Hill and Macpherson, 1954)

THE CHARACTERISTIC CURVES OF MUSCLE

In earlier sections the mechanical condition of active muscle has been specified by four curves

(1) The stress strain curve of the series elastic component $x = f_1(P)$

(2) The tension length curve $P_o = f_2(x)$

(3) The force velocity curve $\frac{dx}{dt} = f_3(P)$

(4) The active state curve $P_o = f_4(t)$

P = force, P_o = isometric force, x = length, t = time, f_1 f_2, etc are to be regarded purely as empirical functions defined by the experimentally determined shapes of the curves

Curve (1) does not depend directly on the contractile machinery Curves (2) and (3) seem to express the properties of the contractile proteins inside the muscle fibres Similar curves are obtained from glycerol extracted muscle fibres activated by ATP, and even from artificial threads of muscle protein which has been in free solution (see e g Weber 1954)

In contrast, curve (4) arises from the mechanism by which the contractile machinery is switched on and off in response to changes of potential at the cell membrane

Each of the curves gives only a partial view of the active muscle, for each of them is made by holding all but two of the parameters constant and observing the relationship between the remaining pair How should one combine the curves when all the parameters are varying at once, as they may do in an actual contraction?

Shortening and the tension length curve The force velocity curve $dx/dt = f_3(P)$ can be written in algebraic form (Hill s equation)

$$dx/dt = (P_o - P)b/(P + a)$$

Since P appears in it as a constant, this equation applies only for small length changes in the region near the flat top of the tension length curve However the equation can be modified to apply at other lengths by arranging that P should vary with muscle length according to the tension length curve

$$dx/dt = [f_2(x) - P]b/(P + a)$$

This equation describes the full range of shortening of the tetanized muscle with fair accuracy (Abbott and Wilkie 1953)

Dynamics of a single twitch Hill s equation can be modified also

to take account of the decline in activity following a simple stimulus by altering P_o both as a function of time and of length

$$P_o(x,t) = f_2(x) \quad f_4(t)/P^*$$

P^* is the original P_o of Hill's equation, i e the tetanic tension at body length

So the equation becomes

$$dx/dt = [f_2(x) \quad f_4(t)/P_o^* - P]b/(P + a)$$

This equation can be tested by inserting experimentally determined values for P_o a, b and for the tension length and active-state curves, then integrating to find how x changes with t for different values of P, i e one predicts the shapes of isotonic

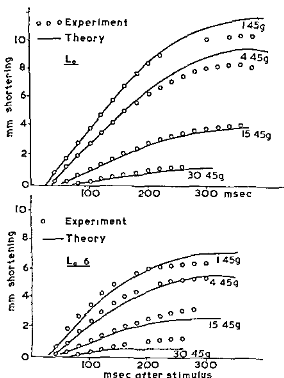


Fig 8 Theoretical and experimental isotonic twitches

twitches against various loads This work (Ritchie and Wilkie, 1955–6) is still in progress Results so far show fair accord between theory and experiment, as illustrated in Figure 8, where the equation is tested at two different initial lengths as well as

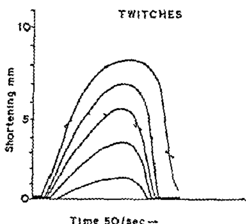


FIG 9 Isotonic and isometric twitches superimposed on the same time scale Isotonic tensions *from above downwards 1 2 5 5 10 20 grams* weight peak isometric tension 28 5 grams weight

at several different loads This equation may therefore be regarded tentatively as the general equation describing the mechanical properties of contracting muscle, from it the various characteristic curves emerge as special cases

Relaxation So far we have confined attention to the phase of contraction The mechanical state of the muscle in the succeeding phase of relaxation is not well understood at present

Figure 9 shows that relaxation is much slower under isometric than under isotonic conditions leading to the apparent paradox that the muscle is able to sustain a given isometric tension long after it has been obliged to drop a weight producing the same tension The explanation for this is not certain but it may be that the muscle proteins retain some of their contracted structure until they are disrupted by forcible lengthening

An examination of the mechanical properties of muscle along these lines should make possible a more penetrating analysis of the various factors which influence contraction Many drugs

alter only the active state curve temperature change alters both the active state curve and the force velocity curve while the tension length curve is more or less independent of external influences The curves thus appear to reflect separately the properties of separable parts of the contractile machinery

REFERENCES

Abbott B C and Ritchie J M (1951) *J Physiol* **113** 333

Abbott B C and Wilkie D R (1953) *J Physiol* **120** 214

Aubert X (1956) *Le couplage enérgetique de la contraction musculaire* Brussels Éditions Arscia

Fenn W O and Marsh B S (1935) *J Physiol* **85** 277

Goffart M and Ritchie J M (1952) *J Physiol* **116** 357

Hill A V (1938) *Proc Roy Soc* B **126** 136

Hill A V (1940) *Proc Roy Soc* B **128** 263

Hill A V (1949) *Proc Roy Soc* B **136** 405

Hill A V (1951a) *Proc Roy Soc* B **138** 329

Hill A V (1951b) *Proc Roy Soc* B **138** 343

Hill A. V and Macpherson L (1954) *Proc Roy Soc* B **143** 81

Lammers W and Ritchie J M (1955) *J Physiol* **129** 412

Macpherson L and Wilkie D R (1954) *J Physiol* **124** 292

Polissar M J (1952) *Amer J Physiol* **168** 766

Ritchie J M (1954a) *J Physiol* **124** 605

Ritchie J M (1954b) *J Physiol* **126** 155

Ritchie J M and Wilkie D R (1955) *J Physiol* **130** 488

Ritchie J M and Wilkie D R (1956) In course of publication

Szent Gyorgyi A (1953) *Contraction on Body and Heart Muscle* New York Academic Press

Weber H H (1954) In *Progress in Biophysics* **4** London Pergamon Press

Wilkie D R (1950) *Electronic Engineering* October p 435

Wilkie D R (1950) *J Physiol* **110** 249

Wilkie D R (1954) In *Progress in Biophysics* **4** London Pergamon Press

Wilkie R D (1956) *J Physiol* In press

XVIII

Proteins in Muscular Contraction

S V PERRY

To understand the role of the muscle proteins in contraction it is necessary to be able to describe the marked changes which occur in muscle tissue during activity in terms of the proteins themselves Unfortunately we are not yet able to do this, but in recent years some progress towards this goal has been made and I wish in this lecture to relate our knowledge of the muscle proteins to the structure of the cell as a whole and in particular to those morphological components within the cell which are responsible for contraction

The cytoplasm of cells from smooth, cardiac and skeletal muscle tissues contains large numbers of longitudinal structures known as myofibrils These structures have long been recognized as the site of the contractile process and the study of muscle has been largely devoted to the study of the myofibril itself as a morphological unit, or to substances derived from it Apart from the myofibrils the skeletal muscle cell contains the usual formed elements such as nuclei, glycogen fat granules, endoplasmic reticulum and lipoprotein granules (the larger of which correspond to mitochondria and which are perhaps best referred to collectively as sarcosomes) Soluble cytoplasm known as the sarcoplasm surrounds all these formed elements and fills up the remaining spaces in the cell (Figure 1)

Although there is no evidence that formed elements other than the myofibrils have any special function in contraction, it is now clear that they have indirect roles to play In the mitochondria are localized the enzyme systems by means of which oxidative processes are harnessed to produce adenosinetriphosphate

(ATP), whereas the anaerobic production of this substance takes place in the soluble sarcoplasm where the enzymes of glycolysis are found The relative importance of these two systems in providing the fuel for the contractile activity of the

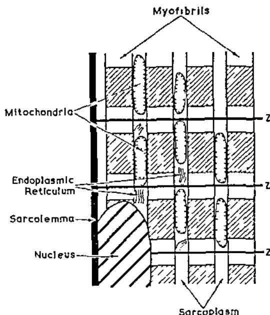


FIG 1 Schematic representation of the skeletal muscle cell There is a wide variation in the number and size of the sarcosomes found in different skeletal muscle cells In the diagram the mitochondria are shown to be relatively abundant as in a highly oxidative tissue such as pigeon breast muscle In some mammalian muscles the sarcosomes are smaller and may be associated with the I band

myofibril is reflected in the morphological appearance of the muscle Tissues of high oxidative activity such as cardiac muscle and the wing muscles of insects and of birds contain numerous large mitochondria whereas in the skeletal muscles of most mammals the mitochondria are much smaller and less abundant

Since the fact that about 80 per cent of the dry weight of muscle consists of protein suggests that the contractile system is built up from this substance it is not surprising that the muscle

proteins have been intensively investigated From the work of a number of investigators (Halliburton, 1887, Von Furth, 1895, 1919, Weber, 1925, 1927, Weber and Meyer, 1933) it was apparent that two main protein fractions could be obtained from skeletal muscle tissue The fraction obtained by extracting minced muscle with water or solutions of low ionic strength (<0 15) was known as the myogen fraction and was later found to contain all the enzymes necessary to convert glycogen into lactic acid When the extraction was carried out at higher ionic strength (>0 5) large amounts of a globulin, myosin, which gave rather a viscous solution, was obtained in addition to the myogen fraction It was presumed that myosin was derived from the myofibril—a view which has been amply confirmed by the study of isolated myofibrils Also it is now realized that solutions of low ionic strength simply extract the soluble sarcoplasm, whereas to bring the proteins of the myofibril into solution higher salt concentrations are required to break down the forces which bind the protein components together in this structure

Subsequent investigations of the myofibrillar protein fraction indicated that in addition to myosin two other proteins, namely actin (Straub, 1942, 1943 Szent Gyorgyi, 1945) and tropomyosin (Bailey, 1946 1948) were present Any understanding of the role of these substances in contraction requires knowledge of their localization in the myofibril and consequently the discussion which follows will be primarily concerned with this aspect and with the interaction of the myofibril and ATP

Structure of the Myofibril

The skeletal muscle myofibril at equilibrium length is characterized by two main bands—the I and A bands The A band, which is usually slightly longer than the I band in living muscle (A F Huxley and Niedergerke 1954) contains the bulk of the protein. It can be seen as a dark band when viewed with ordinary light but in polarized light the A band appears light as it is about ten times as anisotropic as the I band A number of other cross-bands and striae which have been recognized in the skeletal myofibril are indicated in Figure 2 Of these the Z line is a

prominent feature bisecting the I band and there is evidence that it runs continuously across the cell binding the myofibrils to each other and finally fusing with sarcolemma (Draper and Hodge, 1949) The only other banded feature which will be discussed here and in which changes have been observed during contraction and stretch, is the H or Hensens disc This is a

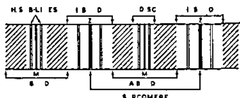


Fig 2 Diagram showing cross bands and lines of the skeletal myofibril

rather broad band of lower protein density which appears in the centre of the A band when muscle is stretched (Hanson and H E Huxley, 1955), and which according to some authors is not readily recognized in myofibrils at equilibrium length

The early histologists notably Kolliker (1888), suspected that the myofibril was built up from fine longitudinal filaments and the application of the electron microscope to the study of the ultra structure of muscle has amply confirmed these views These first electron microscope studies seemed to indicate that the myofibril was built up of parallel filaments running continuously through many sarcomeres The filaments appeared to be 100–200 Å in diameter and to have a regular longitudinal periodicity of 250–400 Å Cross bands were considered to arise from the overlaying of other proteinacious materials, that occurring in the A band for instance was called the A substance

It appears however that the fine structure of the myofibril is more complex than was originally thought for the study of thin cross sections with improved techniques has provided evidence for at least two types of filaments in the myofibril (H E Huxley 1953 Hanson and H E Huxley, 1955) These workers consider that in the A band there are protein filaments of 110 Å diameter which increase to 140 Å where they pass through the

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cent of the total protein consists of actin and myosin and the remainder is made up of tropomyosin and possibly some other proteins not yet characterized In the latter group would be included proteins of which cross striae such as the Z line for example are composed, and those which might be presumed to be present to form a framework of stroma to support and bind the contractile proteins Certainly an insoluble residue remains behind after myofibrils are extracted with solutions which would be expected to bring the recognized myofibrillar proteins into solution (Perry, 1953) Hanson and H E Huxley (1955) have some microscopic evidence that such material is present in the myofibril

TABLE I Size and shape of the molecules of proteins obtained from the rabbit skeletal myofibril Data taken mainly from that collected by Bailey (1954)

Protein	Molecular weight	Thickness (Å)	Length (Å)
Myosin	420 000	25	2,300 –1,500
Tropomyosin	53 000	~15	~400
Actin (monomer)	~70 000	~24	~290
Actin (dimer)	~140 000	~24 (?)	~580

It should be emphasized that the myofibril consists of a con centrated gel containing an average 15–20 per cent protein and will therefore constitute a comparatively rigid structure The surrounding sarcoplasm may be even more concentrated with respect to protein (A F Huxley and Niedergerke 1954) but as the proteins are in solution it will form a much less viscous system

(*a*) *Myosin* Myosin, which accounts for about 45 per cent of the total intracellular protein of skeletal muscle is a globulin of high molecular weight (see Table 1) At pH 7 it is insoluble at ionic strength (I) = 0 05 but at higher ionic strength (~0 5) gives a viscous birefringent solution Recent investigations (Laki and Carroll, 1955) suggest that the molecular weight is about 420 000, which value is lower than that previously reported (Weber and Portzehl 1952) Furthermore physical investiga tions indicate that the molecule is very asymmetric—a property which is of importance in its structural and contractile roles

H space Lying between these A filaments and forming an inter locking hexagonal array with them are finer filaments of 40 Å *These fine filaments do not appear to be present in the H space* but extend into the I band and are known as the I filaments It

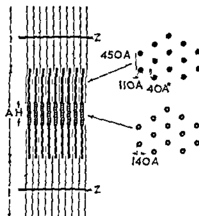


Fig 3 Scheme for the fine structure of the skeletal myofibril After Hanson and H E Huxley (1953 1955)

has been postulated (Hanson and H E Huxley, 1955) that the actin filaments are joined across the H space by fine extensible filaments of protein, the S filaments Such a scheme for the fine structure of the myofibril is illustrated in Figure 3

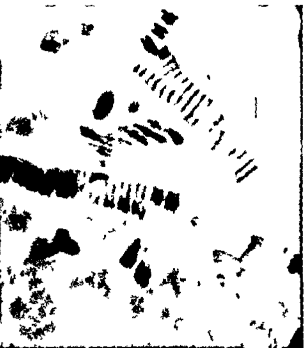
Methods for the preparation of myofibrils free from other formed elements and sarcoplasm (Schick and Hass, 1949, Perry, 1951, 1953, Perry and Grey 1956) which will contract and *simultaneously hydrolyse* ATP have much facilitated study of the function and localization of the myofibrillar proteins Before relating the latter to the structure of the myofibril it is necessary to say something of the properties of the proteins themselves

Proteins of the Myofibril

Analyses of the isolated myofibril (Perry 1952) indicate that it consists almost entirely of protein Very small amounts of fat nucleic acids and inorganic material are also present but it is not possible to say at this stage whether the two former substances really form part of the structure or are merely adventitious con taminants arising during the preparation Probably 80–85 per



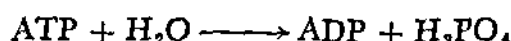
(a)



(b)

FIG 4 (a) Myofibril freshly isolated from rabbit skeletal muscle Mag × ,00 (b) Myofibrils after exhaustive extraction with 0 0,8 borate buffer pH 7 1 which extracts tropomyo in and actin in amount representing about 2, per cent of the total myofibrillar protein Mag × 2,00

A property of myosin which has greatly influenced our concepts of the biochemical basis of contraction is its adenosine triphosphatase (ATPase) activity The association of this enzyme with myosin was first demonstrated by Engelhardt and Ljubimowa (1939) and since that time many efforts have been made to separate the activity from the myosin, but the evidence available today indicates that the enzymic activity is a unique feature of the myosin molecule and not due to a contaminating protein Purified myosin splits off the terminal phosphate from ATP, a process which is greatly activated by calcium



$$ATP + H_2O \longrightarrow ADP + H_3PO_4$$

(*b*) *Tropomyosin* Although tropomyosin is the most recently discovered myofibrillar protein it is perhaps the best characterized for it can be crystallized and lends itself to rigorous purification on account of its great stability compared to myosin or actin Previous studies (Perry, 1953) on isolated myofibrils indicated that tropomyosin represents about 4 per cent of the total protein, but reinvestigation (Corsi and Perry, 1956) has indicated that there may be very much more of this substance present than was previously thought (probably about 12 per cent) As yet there is no indication of the function or localization of tropomyosin *in situ*, but it has been suggested (Kominz, Hough, Symonds and Laki, 1954) as an extension of some earlier ideas of Bailey (1948) that the myosin monomer is built up from units of actin and tropomyosin

(*c*) *Actin* The discovery of actin followed from the work of Szent Gyorgyi and collaborators who noted that when muscle was extracted overnight with salt solutions, myosin preparations (myosin B) were obtained which possessed high viscosity Addition of ATP to such solutions produced an immediate drop in the viscosity which rose again to the original value when the ATP had been hydrolysed Similar observations were made by the Needhams and collaborators (J Needham Kleinzeller, Miall Dainty, D Needham and Lawrence 1942) working independently Subsequent work by Straub (1942 1943) resulted in the isolation of actin which was considered to combine with myosin to form the complex actomyosin (myosin B) At

that time the fall in viscosity of actomyosin which ATP pro duced was explained as being due to the action of the nucleotide in dissociating the complex into actin and myosin, on complete breakdown of the ATP the complex would be reformed with the consequent return of the viscosity to the original high level

Actin represents about 15 per cent of the intracellular muscle protein and as extracted by the method of Straub (1943) it is obtained in the so called globular form (G actin) which forms a solution of low viscosity On addition of salt to solutions of G actin it is converted to the fibrous form (F actin) which combines with myosin to give actomyosin with the properties described above This polymerization of actin as it is described possesses certain unusual features in that there are strong sug gestions that small amounts of ATP which appear to be bound to G actin, undergo dephosphorylation during the formation of F actin (Straub and Feuer, 1950, Laki, Bowen and Clark, 1950) The polarization fluorescence studies of Tsao (1953) have thrown some light on the mechanism of the polymerization process

(*d*) *Actomyosin* Although the effect of ATP on actomyosin solutions was the first clear indication that ATP could produce a physical change in a protein system derived from the myo fibril this effect is not strictly analogous to contraction If how ever actomyosin is precipitated in the form of a thread on the addition of ATP under the correct ionic conditions the thread shortens down to $\frac{1}{4}$ or $\frac{1}{8}$ of its original length The acto myosin thread shortens isodimensionally as the protein fila ments of which it is composed are randomly oriented whereas in the myofibril they all run parallel to the axis of shortening and consequently the myofibril contracts in the anisodimen sional manner characteristic of living muscle A model which is more comparable with the myofibril can be produced by orientating the proteins in these synthetic threads but the protein concentration of actomyosin threads in general tends to be low and they are not capable of developing very high tensions on the addition of ATP The glycerated fibre (Szent Gyorgyi 1949) is a much more satisfactory model for on addition of ATP ten sions are developed which are very comparable to those obtained

myosin in the light of the present views of the nature of the band changes occurring during contraction (see below) Recently Corsi and Perry (1956) have reinvestigated the protein fraction extracted from isolated myofibrils on treatment with 0 078 M borate buffer, pH 7 1 (Perry, 1953) After 10–20 days extraction of myofibrils prepared from fresh muscle ~25 per cent of the total protein passes into solution and the myofibril takes on the characteristic appearance shown in Plate XXV, Figure 4*b* [1] The I band is extremely faint, the Z having disappeared alto gether, whereas the H space becomes wider and much more distinct than it appeared in the freshly prepared myofibril (see Figure 4*a*) The soluble protein fraction obtained under these conditions consists mainly of tropomyosin and a form of inactive actin which is different in properties from both the F and G forms of this protein Myosin does not pass into solution and the ATPase activity of the myofibril falls off very little during the extraction These investigations show that (1) there is very little myosin in the I band, (2) myosin is probably not distributed evenly in the A band in myofibrils isolated from fresh muscle

Changes in the Myofibril during Contraction

A complete description of the function of the myofibrillar pro teins requires in addition to a knowledge of their localization in the myofibril an understanding of the band changes occurring during contraction Due to the technical difficulties involved descriptions given by histologists have been somewhat conflict ing Recent studies on living single fibres with the interference microscope (A F Huxley and Niedergerke 1954) and on iso-lated myofibrils from glycerated muscle made to contract by the application of ATP (Hanson and H E Huxley 1955) are not subject to some of the errors which have complicated earlier studies The latter two groups of workers have concluded that when muscle contracts to 65–70 per cent of the rest length (i e over the physiological range) the A band remains virtually un changed in length whereas the I band shortens When more extensive shortening takes place the I band disappears and the edges of the A band make contact with the Z line to give the

[1] This plate will be found facing p 320

in living muscle Glycerated fibres are made by fixing strips of fresh rabbit psoas at the resting length and storing them in 50 per cent (v/v) aqueous glycerol for several days at $-10°$ This procedure washes out the soluble proteins, much of the original ATP, and leaves a kind of contractile skeleton of the muscle cell The myofibrils are oriented and held in position in the cell just as they are *in vivo* Such preparations have been widely used as model systems for the study of contraction and relaxation

Localization of Proteins in the Myofibril

On the basis of studies of the birefringence of isolated myosin and whole muscle Weber (1934) suggested that there was a concentration of this protein in the A band It had been noted by several workers that the intensity of the A band fell during the extraction of myosin but direct demonstration that most of the myosin was concentrated in the A band was provided by the independent investigations of Hasselbach (1953) and Hanson and Huxley (1953) Hasselbach showed that when myosin free from actin was extracted from fresh muscle the A band was no longer apparent on electron microscope study of the myofibrillar residues Hanson and Huxley observed somewhat similar effects when myofibrils isolated from glycerated muscle were perfused with solutions which selectively extracted myosin The latter workers did point out, however, that the centre of the A band the H disc, was not so readily extracted under these conditions

After extraction of the myosin long continuous filaments could be seen and the postulate that these consisted of actin was supported by the fact that on treatment with procedures for the extraction of actin these filaments disappeared As a result of these findings Hanson and H E Huxley (1953) suggested that the A filaments in their model consisted of myosin, whereas actin was localized in the I filaments

The possibility that the myosin is localized in the A band is not apparently acceptable to all workers (see A G Szent Gyorgyi Mazia and A Szent Gyorgyi, 1955), certainly it does present some difficulties in explaining the contractile role of

Hill, 1955) to suggest that the binding of ATP to the contractile protein system is sufficient to produce contraction and that con traction itself is independent of dephosphorylation of ATP Morales *et al* (1955) consider that the contractile element (actomyosin) is kept fully extended due to the mutual repulsion of positive changes distributed along the length of the element (Figure 5) On addition of ATP, which exists in solution under physiological conditions mainly as a negatively charged ion (ATP^{4-}), the nucleotide is bound and neutralizes the positive charge on the contractile element so that the extending electro static force disappears Consequently the actomyosin element will shorten under the influence of thermal agitation forces (see Figure 5)

From time to time it has been suggested that the splitting of ATP by the actomyosin system involves phosphorylation of the protein The various mechanisms for contraction of phosphory-lated myosin which have been suggested range from that pro posed by Riseman and Kirkwood (1948), who postulated that phosphorylation of hydroxyamic acids would modify the ex tending electrostatic force so that entropic contraction of the type adopted by Morales *et al* (1955) would take place to those favouring a mechanism involving formation of covalent links between different points on the polypeptide chain of myosin in such a way that the chain must fold (Binkley 1945 Weber 1955) Such a mechanism is illustrated in Figure 6

Using ^{32}P labelled ADP Koshland Budenstein and Kowalsky (1954) were unable to demonstrate the formation of a phos phorylated myosin intermediate during the hydrolysis of ATP They concluded that if such an intermediate existed it was of transitory nature but Morales *et al* (1955) consider that Kosh land s results are consistent with a binding contraction rather than a phosphorolytic cleaving contraction mechanism The latter conclusion is however, not unequivocal as Weber (1955) has recently reported evidence for the existence of a phosphory lated myosin intermediate during the interaction of myosin and ATP

Although it is apparent from the above discussion that an adequate description cannot yet be given of the relation of the

appearance of reversal of striation which is characteristic of strongly contracted muscle On stretching the myofibril over the range within which length changes are reversible the length of the A band is likewise unchanged for extension appears to be confined to the I band only

Enzymic Activity of the Myofibril

Of the three well characterized myofibrillar proteins only myosin has so far been demonstrated to possess any enzymic activity, namely ATPase Consequently the intact myofibril has marked ability to liberate inorganic phosphate from ATP, but it should be stressed that there exist considerable differences in properties, particularly with respect to the activating effect of ions, between the myofibrillar ATPase and myosin when they are studied under conditions comparable to those existing in the cell For instance whereas only calcium will activate myosin ATPase the myofibrillar enzyme is activated both by calcium and magnesium The isolated myofibril freed from sarcoplasm usually possesses 5 adenylic deaminase and myokinase activity (see Perry 1956) but these enzymes do not appear to play any part in contraction and are probably contaminants not readily removed by the repeated washing procedures used during the preparation of myofibrils

Assuming that the energy made available on the hydrolysis of ATP provides the energy for contraction one might expect that contraction and dephosphorylation would be closely linked processes Many workers (Weber and Portzehl, 1952, 1954, Bendall, 1953a Bozler and Prince, 1953) have provided evidence that there is a close correlation between the level of ATPase activity and the rate of shortening in model systems of actomyosin threads or glycerated fibres Somewhat different evidence supporting the same view has been obtained by Perry (1954) from the coupled creatine phosphokinase and myofibrillar ATPase systems Nevertheless several reports are to be found in the literature which throw doubt on the view that dephosphorylation is a necessary requirement of contraction Such examples and certain physico chemical considerations have led Morales and his collaborators (see Morales Botts, Blum and

band which apparently do not change in length Some evidence of density changes within the A band during ATP induced con traction of myofibrils isolated from glycerated muscle has been reported (Hanson and Huxley 1955) and possibly these may reflect changes within the A filaments

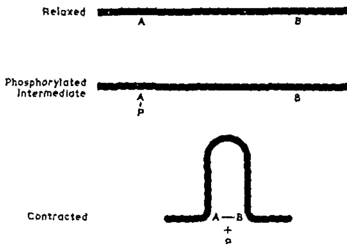


Fig 6 Scheme for contraction involving phosphorylation of the contractile element A and B are groups which lie some distance apart on the contractile element A is phosphorylated and when activated in this way it forms a bond with B Inorganic phosphate is simultaneously liberated the element is folded and contraction results

Biochemical analyses of the changes occurring during the phases of a single twitch in living muscle offer an approach to the problem of studying the chemical events which accompany contraction *in situ* The technical difficulties are considerable but with the aid of chromatographic methods some progress has been made The recent results of Fleckenstein, Janke Davies and Krebs (1954) indicate that inorganic phosphate is produced during a single twitch but it is not clear from which compound this is derived These workers and, independently Mommaerts (1954) confirm Fleckenstein s (Fleckenstein Janke and Elke, 1954 Fleckenstein Janke Lechner and Bauer, 1954 Fleckenstein and Janke 1953) earlier findings that the level of ATP and ADP is unchanged during a single twitch Whilst it is generally

enzymic to the contractile changes, it seems indisputable that the interaction of ATP with the actomyosin system can cause contraction to take place Until recently contraction had been demonstrated in model systems containing actomyosin and not with either protein alone, yet myosin has usually been considered

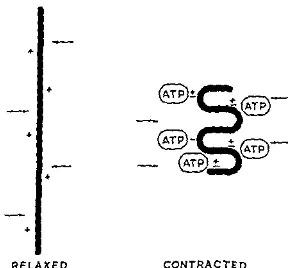


Fig 5 Scheme in which the binding of ATP induces contraction The contractile element is shown extended by the mutual repulsion of positive charges distributed along its length Binding of ATP neutralizes the extending charges and shortening of the element takes place as a result of thermal agitation forces

to be the contractile partner This view is supported by recent experiments of Russian workers (Ashmarin, 1953, Kafiani and Engelhardt, 1953) who have reported that ATP can bring about the contraction of threads made from surface films of actin free myosin This effect was obtained at pH 9 but could be obtained at physiological pH values in the presence of certain dyes and suggests that the role of actin may be to modify the charge distribution on the myosin

It is difficult to reconcile a contractile role for myosin with the changes in striation occurring on contraction if the model proposed by Hanson and Huxley is accepted This would mean that moderate contraction involves a shortening of the I (actin) filaments mediated in some way by the myosin filaments in the A

activity associated with the shortening of glycerated fibres during relaxation the ATPase activity is low It follows therefore that ATP has a dual function when interacting with the actomyosin system, namely

(1) contracting action associated with a high rate of ATPase activity,

(2) relaxing or plasticizing action associated with the low rate of ATPase activity which occurs in the presence of relaxing factor

As yet there are no clear ideas on the nature and action of the relaxing factor although relaxing activity has been claimed for a number of enzymes e g myokinase (Bendall 1954), creatine phosphokinase (Goodall and Szent Gyorgyi 1953, Lorand, 1953) as well as for unphysiological substances such as inorganic pyrophosphate (Weber 1951, Bozler 1951, Bendall, 1953b) and ethylenediamine tetraacetate (Bozler, 1954 Watanabe, 1955)

A study of the properties of the hydrolysis of ATP by isolated myofibrils (Perry and Grey, 1956) has shown that the inhibition obtained by higher ATP concentrations is markedly dependent on the magnesium concentration when this cation is the activator (see Figure 7) This effect is a feature of magnesium activation and is not obtained when calcium is the activator Hence at a given ATP concentration when adequate magnesium is present the rate of ATP hydrolysis is high but if the magnesium is removed from the system by various complexing agents the ATPase activity falls to a low level due to a relative excess of ATP This condition of substrate inhibition is considered to be characteristic of relaxation in glycerated models and it is suggested that the role of the relaxing factors is either to bind magnesium or to maintain the ATP at a high concentration so that the ATP is in relative excess and its relaxing action becomes dominant Certain properties of the substrate-inhibited magnesium activated ATPase support this view for example the effective relief of substrate inhibition by low concentrations of calcium is paralleled by the effect of similar concentrations of calcium in inhibiting relaxing factor action (Bozler 1952 Bendall 1953a)

agreed that the ATP level may fall on more prolonged activity, other workers (Mommaerts and Rupp 1951, Munch Petersen, 1953) have claimed that a fall in ATP and increase in ADP can also be demonstrated after a single twitch If the results of Fleckenstein *et al* and Mommaerts are valid *they raise the question* whether some substance other than ATP is the source of the inorganic phosphate produced in contraction There is no evidence as to what this substance might be, if indeed it exists at all the other nucleoside triphosphates (inosinetriphosphate, uridinetriphosphate and guanosinetriphosphate) which actomyosin readily hydrolyses have come under suspicion but some results of Hasselbach (reported by Weber, 1955) on their ability to induce the relaxation of glycerated fibres appear to exclude these substances Certainly *in vitro* ATP will induce contraction of the isolated myofibril which is completely free from the other nucleoside polyphosphates

Relaxation

Although this lecture is intended to deal with the muscle proteins and contraction it would not be out of place to conclude with a few remarks about their role in relaxation If the isolated myofibril is treated with ATP of the same concentration as that found in the cell and in a similar ionic environment, it hydrolyses the nucleotide rapidly and contracts In resting muscle the rate of inorganic phosphate production is very low, suggesting that there is present in living muscle some factor which inhibits the myofibrillar ATPase activity and thus prevents contraction

The work of Marsh (1952) Bendall (1953a), and Bozler (1951) has shown that indeed this is the case This substance, which is known as the relaxing factor (there may be two components, see Kumagai Ebashi and Takeda, 1955), is considered to be effective in resting muscle but somehow its inhibitory effects are lifted during contraction so that the ATPase activity rises and the myofibril contracts

In the presence of partly purified preparations of the relaxing factor, glycerated fibres which had previously been contracted by the addition of ATP will relax if ATP and magnesium are present Furthermore in contrast to the high level of enzymic

REFERENCES

Ashmarin I P (1953) *Biokhimiya* **18** 71
Bailey K (1946) *Nature Lond* **157** 368
Bailey K (1948) *Biochem J* **43** 271
Bailey K (1954) *The Proteins* ed H Neurath and K Bailey Academic Press New York, Vol 2 p 951
Bendall J R (1953a) *J Physiol* **121** 232
Bendall J R (1953b) *Nature Lond* **172** 586
Bendall J R (1954) *Proc Roy Soc* B **142** 409
Binkley F (1945) *Science* **102** 477
Bozler E (1951) *Amer J Physiol* **167** 276
Bozler E (1952) *Amer J Physiol* **168** 760
Bozler E (1954) *J gen Physiol* **38** 53
Bozler E and Prince J T (1953) *J gen Physiol* **37** 53
Corsi A. and Perry S V (1956) To be published
Draper M H and Hodge A J (1949) *Austr J exp Biol med Sc* **27** 465
Engelhardt V A. and Ljubimowa M N (1939) *Nature Lond* **144** 668
Fleckenstein A. and Janke J (1953) *Pflugers Archiv* **258** 177
Fleckenstein A Janke J and Elke M (1954) *Arch exp path Pharmakol* **221** 404
Fleckenstein A. Janke J Davies R E and Krebs H A. (1954) *Nature Lond* **174** 1081
Fleckenstein A. Janke J Lechner G and Bauer G (1954) *Pflugers Archiv* **259** 246
Goodall M C and Szent Gyorgyi (1953) *Nature Lond* **172** 84
Halliburton W D (1887) *J Physiol* **8** 133
Hanson J and Huxley H E (1953) *Nature Lond* **172** 530
Hanson J and Huxley H E (1955) *Symposia of the Society for Experimental Biology* **9** 228
Hasselbach W (1953) *Z f Naturforsch* **8b** 449
Huxley A F and Niedergerke R (1954) *Nature Lond* **173** 971
Huxley H E (1953) *Biochim biophys Acta* **12** 387
Kafiani W A and Engelhardt V A (1953) *Doklady Akad Nauk S.S.S R* **92** 385
Kolliker A (1888) *Zeit Wiss Zool* **47** 689
Kominz D R. Hough A. Symonds P and Laki K (1954) *Archiv biochem biophys* **50** 148
Koshland D E Budenstein Z and Kowalsky A (1954) *J biol Chem* **211** 279
Kumagai H Ebashi S and Takeda F (1955) *Nature Lond* **176** 166
Laki K Bowen W J and Clark A. M (1950) *J gen Physiol* **33** 437
Laki K and Carroll W R (1955) *Nature Lond* **175** 389
Lorand L (1953) *Nature Lond* **172** 1181
Marsh B B (1952) *Biochim biophys Acta* **9** 247

Conclusion

Although considerable advances have been made in describing the structure of the contractile units in terms of their protein components, much remains to be done A great deal of bio chemical knowledge is available and it is fair to say that the

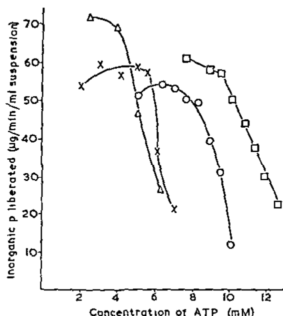


Fig 7 Effect of $MgCl_2$ concentration on the inhibition of the myofibrillar ATPase activity by excess substrate Incubations were carried out in 0 05 M trishydroxymethyl amino methane buffer pH 7 4 for 5 min at 20 5 C

△ 2 5 mM $MgCl_2$
× 5 mM $MgCl_2$
○ 7 5 mM $MgCl_2$
□ 10 mM $MgCl_2$

muscle cell provides one of the outstanding examples of pro gress towards the aim of integration of biochemical function with morphological structure Nevertheless the nature of the fundamental relationship between chemical events and mech anical changes has yet to be determined What is clear is that the normal structional changes in the myofibril are determined by enzymic changes related to both myofibril and sarcoplasm

XIX

Observations on the Excitable Cortex in Man

J A V BATES

At the end of the last century there was a unique convergence of thought and discovery in the fields of comparative anatomy, physiology, pathology, histology and clinical neurology, and there emerged a new set of beliefs concerning the organization of the efferent side of the central nervous system It was postulated that motor centres existed in the cerebral cortex centres wherein the faculty of voluntary movement resided centres evolutionarily more recent than spinal motor centres, centres wherein were represented movements in the most differentiated degree, centres from which voluntary nervous impulses were discharged via the pyramidal pathway This scheme, which I shall refer to as the classical hypothesis was proposed notably by Ferrier Gowers and Schaefer and with important reservations by Hughlings Jackson It was opposed by some clinicians notably Bastian and most Continental neurophysiologists There is a great deal to be learnt from study of the various controversies that followed but the person whose views most concern us today studiously kept apart from the polemics and was content to contribute a few vital facts of observation from an experience which no one before or since has rivalled in its scope—his name of course was Sherrington

During the past five years at the National Hospital for Nervous Diseases Queen Square, London thanks to the help given by Dr Carmichael, Mr McKissock and their various assistants

MOMMAERTS W F H M (1954) *Nature Lond* **174** 1083
MOMMAERTS W F H M and RUPP J C (1951) *Nature Lond* **168** 957
MORALES M F, BOTTS J BLUM J J and HILL, T L (1955) *Physiol Rev* **35** 475
MUNCH PETERSEN A (1953) *Acta physiol scand* **29** 202
NEEDHAM J KLEINZELLER A MIALL M DAINTY M, NEEDHAM D M and LAWRENCE A S C (1942) *Nature Lond* **150** 46
PERRY, S V (1951) *Biochem J* **48** 257
PERRY, S V (1952) *Biochim biophys Acta* **8** 499
PERRY, S V (1953) *Biochem J* **55** 114
PERRY S V (1954) *Biochem J* **57** 427
PERRY S V (1956) *Physiol Rev* **36** 1
PERRY S V and GREY T C (1956) *Biochem J* **64** 184
RISEMAN J and KIRKWOOD J G (1948) *J Amer chem Soc* **70** 2820
SCHICK A F and HASS G M (1949) *Science* **109** 487
STRAUB F B (1942) *Studies Inst Med Chem Univ Szeged* **2** 3
STRAUB F B (1943) *Studies Inst Med Chem Univ Szeged* **3** 23
STRAUB F B and FEUER, G (1950) *Biochim biophys Acta* **4** 455
SZENT GYORGYI A (1945) *Acta physiol scand* **9** suppl 25
SZENT GYORGYI A (1949) *Biol Bull* **96** 140
SZENT GYORGYI A G MAZIA D and SZENT GYORGYI A (1955) *Biochim biophys Acta* **16** 339
TSAO T C (1953) *Biochim biophys Acta* **11** 227
VON FURTH O (1895) *Arch exp path Pharmakol* **36** 231
VON FURTH O (1919) *Ergebn Physiol* **17** 363
WATANABE S (1955) *Arch biochem Biophys* **54** 559
WEBER H H (1925) *Biochem Zeit* **158** 443 473
WEBER H H (1927) *Biochem Zeit* **189** 407
WEBER H H (1934) *Erg Physiol* **36** 109
WEBER H H (1951) *Z Electrochem* **55** 511
WEBER H H (1955) Conferences et Rapports 3rd International Congress of Biochemistry Brussels p 356 Ed C Liebecq Vaillant Carmanne Liege
WEBER H H and MEYER K (1933) *Biochem Zeit* **266** 137
WEBER H H and PORTZEHL H (1952) *Adv in Protein Chem* **7** 161
WEBER H H and PORTZEHL H (1954) *Progress in Biophysics and Biophysical Chemistry* **4** 60

Sherrington however, commented on it indirectly from his experience of stimulating over forty chimpanzees (Leyton and Sherrington, 1917) He noticed that particular movements that he could readily obtain in one animal could not be obtained in another animal and vice versa, and he discussed the extent to which these differences could reasonably be attributed to accidents of technique or anaesthesia, and more especially to the differences in configuration of the cortical gyri in different animals—for about one third of the excitable cortex in any animal is normally buried in sulci He concluded that these various factors were insufficient to account for the differences between different animals and it seemed therefore to him that an individuation of response must be postulated I have made observations on four cases where we have re explored the motor region on a second occasion some months later (Bates 1953b) It has been found that the repeatability of the excitable points in a topographical sense is very high and that particular individual characteristics in the response seen on the first occasion are repeated on the second In other words it seems in man also that both the anatomical fixity and the details of movement differ in a consistent way between individuals

Now the conventional idealized diagram of the cortex with the words Face, Arm Leg inscribed on the precentral gyrus has been developed by Penfield s artist into the well known homunculus Penfield in this room three years ago (Penfield 1954) reminded us that this is no more than a mnemonic to recall the peripheral connexion of each part of the gyrus But I think three other points about the homunculus should be stressed First, that as a summary it discards a large amount of data for the movements which were actually observed are nowhere recorded Second that we are in the hands of the artist rather than the statistician for this concept of the average for the amount of topographical variation between individuals as shown by Penfield s own protocols is very considerable Third that there is a danger that this average is thought of as having a real existence in each of us so that departures from it in an individual protocol are put down to insufficiently thorough exploration or other incidents of technique Sherrington would not

I have had an opportunity to make observations on the excitable motor cortex exposed at operation on man, and I shall discuss certain observations which are relevant to the foundations of the classical hypothesis of cortical motor centres Although these observations on man are rather fragmentary, I think they are significant because they seem to be complementary to some observations which Sherrington made under very different conditions on monkeys and apes

The technique has been given in more detail elsewhere (Bates, 1953a), but in brief we have stimulated the cortex electrically in sixty cases of various types of cerebral disease, forty of which have had a hemispherectomy There have also been occasions when we have felt justified in stimulating the cortex when there was no obvious adjacent pathology The patients have all been very lightly anaesthetized with nitrous oxide, oxygen and Pethedine A 2 mm bipolar stimulator has been used delivering interrupted DC from a low impedance source in the form of 50 square pulses per second of 4 msec duration each The cortex is stimulated for 3 sec at each application and the excitable points are marked by numbered tickets Cine films are taken of all the motor responses, and study of these forms the basis of my material [1]

Repeatability of Responses

Now before we face the problem of describing the responses that follow the stimulus and interpreting them, there is a question which naturally arises at the very outset—are the responses to stimulation repeatable? It has long been known that if you repeatedly stimulate the same cortical point under certain optimum conditions, the motor response remains unchanged But the more significant question is—what is the long term repeatability? That is to say, how do the motor map and the responses at one exploration compare with those at a second exploration some months later? There is surprisingly little in the literature on this in view of its importance in fact I have not a single series of animal experiments specifically designed to answer it

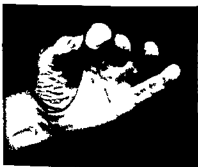
[1] This lecture was illustrated with cine films but single frames from films make unsatisfactory illustrations and none have been included here



(*a*)



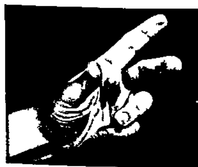
(*b*)



(*c*)



(*d*)



(*e*)



(*f*)

FIG. 1

accept this assumption for the chimpanzee and it would not appear to hold for man

On the evidence from man it seems that the map of the excitable points and the details of the responses are as individual as the face or fingerprint and hence it is not unreasonable to suggest that we may be dealing with a system with a pronounced genetically determined element The particular movements obtained in an individual would seem then to be a selection out of a larger class available to the species, similar in fact to his particular blood groups This of course is speculative, but it seems at least that the responses to a single stimulus have a sufficient degree of long term repeatability to make it worth discussing the difficult question of how to describe and interpret the movements observed

Cortical Stimulation and Reflex Movements

Ferrier (1886) considered that he had evoked by stimulation the distinctively voluntary or purposeful movements of his various animals and he even went so far as to suggest that stimulation would evoke any special tricks of movement learnt by the particular animal during its life Clearly his belief in highest motor centres would have been justified if this belief could have been verified Schaefer (1900) supported Ferrier's scheme and published a myogram to illustrate the similarity between voluntary movement and cortically induced movement in the monkey

Sherrington I think was among those who never completely identified themselves with this interpretation He stressed particularly the fractional nature of the movements and would not commit himself to the word purposeful' to describe them We must surely agree that the word purposeful' introduces yet another confusing element, for any movements which successfully achieve a recognizable end can be called purposeful and these would include the escape movements of the spinal frog or the feeding movements of protozoa Clearly any word that is based on a subjective opinion of what may be behind the movement must be discarded in describing it The only approach open to us is to record as accurately as possible what is observed

and afterwards to see if any similar movements or postures are observed under any other condition This was Sherrington's method, and he was struck by the resemblance between the movements he evoked in his animals by cortical stimulation and the movements he evoked by sensory stimulation in the same species of animal under a spinal preparation In 1892 he wrote 'Flexion and adduction of the hallux with extension of the other digits I have frequently seen occur as a spinal reflex movement in the foot of M Rhesus, just as one frequently sees it occur on excitation of the leg area of the hemispheral cortex And he wrote in 1898, Flexion adduction of the thumb [in a monkey] though instanced as an action of peculiarly cortical nature, is really the most frequent and facile pure spinal reflex of the upper extremity, and in more general terms in *The Integrative Action* (1906) The local reflex movements obtainable from the bulbo-spinal animal and the reactions elicitable from the motor cortex of the narcotized animal fall into line as similar series Both consist of the same group We cannot make observation on bulbo-spinal human preparations as he could on the dog and monkey consequently we cannot discuss with the same confidence the nature of motor organization at a spinal level in man But the problem which Sherrington poses is whether or not we can show a resemblance in man between the response to cortical stimulation and certain types of movement which on other grounds we may feel justified in believing are organized at a spinal level

Clinical neurology recognizes two main classes of reflex movement the deep and the superficial The deep reflexes are a muscle twitch caused only by a sudden stretch and localized to the muscle or muscle group stimulated by stretching They are relatively similar from person to person They are normally equal on the two sides of the body and the movements observed are explained by the facts of muscle and bone anatomy The superficial reflexes are in contrast, ill defined and unexplained This group of phenomena includes movements variously called postural reflexes associated movements reflexes of spinal automatism defence reflexes flexor withdrawal reflexes By far the most notorious superficial reflex is the

discrete finger movement, when evoked by cortical stimulation, is evidence of the evocation of a skilled movement Films have been taken of normal infants during the first 48 hours of life when they are awake and relaxed (i e during the few minutes in the 24 hours when they are neither sleeping feeding nor crying), and it is at once apparent that the infant has been born with an abundant supply of discrete finger movement In fact movements of any particular finger can appear more independent of movement of neighbouring fingers than they are in the average adult hand, and this applies more obviously to toe movements

If therefore one considers the discrete finger movements evoked by stimulation, one cannot necessarily assume that one has evoked movements that would not have existed save for consciously directed practice What the growing child acquires is a measure of control over the mechanism for discrete movements he is supplied with, and it is necessary to keep clear the distinction between a mechanism for discrete movement and an ability to control the discrete movement It would be helpful to know whether or not infants born with grossly deficient cerebral development show discrete finger movement since they may be the nearest we ever get to a bulbo spinal preparation I have not yet had the opportunity of filming movements in such a case but from what others have told me it seems likely that these infants at birth do show the same differentiation of finger movement as a normal infant

This digression has been necessary to establish that discrete finger movement when evoked by cortical stimulation is not necessarily evidence of differentiation through practice and we can now continue with the main question provoked by Sherrington s observation on the bulbo spinal monkey These observations arouse a suspicion that in cortical stimulation one is merely activating particular movements or changes in posture that are provided for by nervous arrangements outside the cortex presumably at a spinal level Observations on man give evidence for this of three different kinds

In the first place if these movements are to be looked upon as organized at a spinal level it would be helpful if cortical stimulation actually would evoke the best recognized superficial

Babinski phenomenon, but many others alleged to be of value in clinical neurology have been described They are distinguished from deep reflexes in several important ways As a group they are elicited by a variety of stimuli which include scratching the skin, stretching the skin, slow stretching of muscles Stimulation is effective over relatively wide zones, the responses have a relatively long latency, the movements are more generalized and sometimes bilateral, the superficial reflexes are more susceptible to fatigue and to the influence of the subject s attention, and lastly, they show greater variation in the normal and in particular may not be the same on the two sides of the body Thus a problem arising out of Sherrington's observations is whether or not the movements in response to cortical stimulation in man resemble movements in the general class of superficial reflexes

Let me begin with a negative statement Penfield (1954) has stressed that nothing resembling a skilled movement is ever seen in response to cortical stimulation This raises a question as to what is a skilled movement, but it does seem that nothing resembling a movement which one recognizes as having been acquired by practice and repetition is ever seen in response to cortical stimulation For example, consider a simple movement which is seen from about six weeks onwards in the infant in which the back of the hand the base of the thumb and after hours of practice the tip of the thumb is brought neatly to the mouth This requires a particular co ordinated behaviour of muscle groups acting on the shoulder and elbow, and although it is not uncommon to see stimulation produce movement at both the shoulder and elbow, I have never seen the hand or any part of it brought to the mouth in response to stimulation *If this hand to mouth movement a movement that is practised daily by all of us is not seen one might not expect to see other* less frequently practised movements But skilled is also taken as *synonymous with delicate or discrete, and on this basis it might* be asked—are not discrete movements of the thumb and indivi*dual fingers* in fact movements acquired by practice—are they not movements differentiated out of grosser movements by consciously directed effort in the young child? If this is correct then

middle fingers and this posture has been said to show inherited familial tendencies—from my own observation, about 1 in 10 of the males I can frequently observe adopt this posture involuntarily some time during the day It is also seen in some chronic hemiplegic hands and is illustrated in Gowers s *Textbook of Neurology* from a case of athetosis I have seen this posture produced in two cases from cortical stimulation

Figure 1*c* illustrates an associated extension of the outer three fingers with the thumb and index opposed The little finger is most extended and this posture is seen in some people holding a tea cup It is commonly thought to be an affectation but it is seen in the infant especially at the nine months stage when thumb index opposition begins and I think should be regarded basically as an associated movement occurring in association with the pincer action of the thumb and index One of the commoner cortical response synergies involves extension of the outer three fingers The extension often commences in and develops to a fuller extent in the little finger and it leads to the posture illustrated

Figure 1*d* is of the familiar pointing gesture of the notice board—the fully extended thumb and index and fully flexed third fourth and fifth This posture is the opposite of *c* and is one seen in the outstretched hand in a postural role and in the infant before the nine to twelve months thumb index period as well as during it This line of inquiry started from the coincidence of seeing on the same day this particular hand posture produced by cortical stimulation and the same posture assumed in the fully extended left arm of a footballer photographed at the instant of a strenuous right footed kick

Figure 1*e* is one of the old hand signs used in religious blessing known as the *mano pantea* Occasionally cortical stimulation of the hand area gives no evidence of the thumb index differentiation but instead the index and middle fingers move as a unit and produce this posture in extension

Figure 1*f* with the interphalangeal joints of the fingers extended is the *main figee* or congealed or the *main d accoucher* When combined with some flexion and adduction of the metacarpo phalangeal joints and the wrist it is the hand of tetany

reflex movement, namely the Babinski plantar response, in suitable cases I have previously reported (Bates 1953a) on the results of stimulation of the medial surface of the sound hemisphere in ten cases, and in two of them a response has been observed which closely resembles the crossed Babinski phenomenon That is to say, an up going toe in the hemiplegic foot (which is ipsilateral to the cortex stimulated) together with spreading of the other toes, some flexion of the hip and a flexor toe response on the sound (contralateral)side I have also seen isolated dorsiflexion of the contralateral great toe from stimulation of the internal capsular fibres after hemispherectomy

The second set of evidence to which I would call attention concerns the hand It seems there is a resemblance between certain of the postures which the normal adult's hand is seen to adopt *in the unattended to state* and certain of the postures of the wrist and fingers that follow stimulation of the normal cortex Hand postures are easy enough to observe in daily life though very difficult to record Data is to be found in press photographs of the candid camera type, and to some extent in the literature of gesture and hand sign languages Plate XXVI, Figure 1[1] illustrates some of the postures in question

Figure 1*a* shows the left hand in the position of rest Note that the index is characteristically less flexed than the outer three fingers and note also the upper transverse flexure line which turns upward to end on the web between the index and middle fingers This is also shown in *e* The ending of this flexure line is one of the cardinal distinguishing features of the human hand *in all monkeys and apes it crosses the palm to the* radial border It is concomitant with the aloofness of the index finger from the behaviour of the remaining fingers which Wood Jones (1941) commented on It is relevant to note that this flexure line is present from about the tenth week of foetal life onwards well before individuation of index finger movement by practice could be effective

Figure 1*b* shows a posture which has been described since the days of Ovid as the *manus obscaena* for obvious reasons More usually perhaps *the thumb comes between the index and*

[1] This plate will be found facing p 336

after movements are far less likely to occur But it is not difficult to obtain the smallest discrete movements from stimulation of the fibres as they pass through the internal capsule

Thus from the mere character of the movement or change in posture in an individual case there is little to convince one on the evidence of stimulation that the grey matter is playing a significant role

Let me at this point recapitulate the argument so far The movements evoked by cortical stimulation were originally likened to voluntary or purposeful movements But these labels owe their origin to a pre existing hypothesis of cortical motor function If the hypothesis is questioned, the likeness seems questionable One can readily say what the movements are not like, but so far as I can see only Sherrington has called attention to what they seem to resemble He said they resembled in detailed character and ease of production some of the move ments that you would obtain reflexly by sensory stimulation in the spinal preparation of the same species he also suspected that they have an individuality at least in apes It seems one can get complementary evidence in man which is consistent with his views, although the support is naturally enough, indirect

Sherrington, it will be remembered, observed isolated thumb movement as a pure and facile spinal movement and I have emphasized that newborn infants have a large repertoire of discrete finger movement This does not prove that such move ments are organized at a spinal level but it suggests they may be, and it does establish that they are differentiated from gross movements without deliberate practice Secondly at least one complex response movement widely regarded as a spinal automatism—the crossed Babinski response—can be produced by cortical stimulation in an appropriate human preparation Thirdly, stimulation may provoke certain postures of the wrist and fingers which are characteristic of those adopted involuntarily in normal people and which are variously classified as postural reflex movements associated movement reflexes of spinal automatism Lastly a variety of responses including dis crete finger movement and characteristic hand postures can be

But it is also a not unfamiliar posture in the hand of orators, and since it is also described by patients illustrating the form of their focal epilepsy it is not surprising to see that it is also produced by stimulating the cortex

There is some evidence therefore that so far as the hand is concerned, there may be a similarity between the details of its associated movement and involuntary posturing and the responses to cortical stimulation of the hand area Although we do not know enough of what lies behind these postures to say that they represent the activity of intact neurone organizations at a spinal level, this similarity is relevant to any interpretation of the cortical motor response

The third piece of evidence relevant to Sherrington's observations is of a rather different nature

If we consider how we could test the hypothesis that stimulation gives evidence of cortical motor centres it would be instructive to compare the responses between stimulating the outer layer of the cortex and the fibres leaving it, say in the internal capsule This is tantamount to asking Because stimulation of the cortex produces movement, can you infer that you have demonstrated centres for movement peculiar to the grey matter?' This was the inference of Ferrier and others But a few months after Ferrier s paper appeared (in 1873), Burdon Sanderson (1874) showed that all the movements that could be produced by stimulation of the grey matter in the cat could be produced equally readily by stimulation of the white fibres after the grey matter had been cut away Sherrington (1906) went even further and showed that inhibition of movement could be produced by capsular stimulation

In observations on man Penfield has confirmed Burdon Sanderson s old results and so have I (Bates 1953c) So far as the detailed character of the movement or of the resulting posture is concerned, stimulation of the white fibres and the grey matter gives similar results in a given individual save that when stimulating the capsule the motor disturbance may be more extensive due to intermingling of descending fibres There are however differences Without the grey matter the latency between stimulus and response is invariably short and clonic

a partial hemiplegia of many years duration But there are cases (four out of thirty nine) where such wrist and finger movements as these have remained unchanged in spite of removal of the hemisphere which has been demonstrated to contain excitable motor points It appears from histological examination that the cortex beneath these points has been undisturbed by the disease process I would emphasize that it is not that function returns to these patients by a process of recovery, but that what function they have is never in the least disturbed further by the operation —it is present unchanged on coming round from the anaesthetic And film records confirm the detailed similarity between particular movements they can make to order and movements evoked by stimulation of their cortex which is by now in the pathologist s bottle

These observations, I think, suggest that one of the pillars of the classical hypothesis is not as strong as it seemed for in the excitable motor region ablation and stimulation though normally in a sense complementary in their effects are not invariably so And it is relevant to point out that stimulation and ablation are by no means complementary techniques, taking the normal cortex as a whole Those familiar with Penfield s accounts of his operation will not need me to expand this Excision of a region producing phonation is not followed by permanent speech difficulty of a region producing somatic sensation is not followed by anaesthesia of a region producing complex auditory and visual recall phenomena is not followed by failure to recall subsequently the particular phenomena And more especially relevant, there is a region on the medial surface from which complex movements are evoked which Penfield has called the Supplementary Motor Area Excision of this excitable motor region is not followed by motor deficit None of all this was known to Ferrier and his contemporaries but we cannot ignore it and I believe there are sufficient grounds for suspecting that the pre Rolandic area may be a special case in the sense that the superficial concurrence between stimulation and ablation in that region may be so to speak a major physiological red herring Penfield (1954) has made the suggestion that when motor function partly recovers there is a recovery of precisely

obtained by stimulation of capsular fibres similar to those obtained from the cortex

I submit that these observations, taken together with Sherrington's, naturally lead to the question whether, on the evidence of stimulation alone, there is anything to suggest a higher order of motor representation in the cortex Would not a sufficient hypothesis *on the evidence of stimulation* be this—that there are a set of motor organizations at a spinal level and various nervous pathways are afferent to them one set coming from the skin and deeper structures via the dorsal roots others from the brain? We might look on the cortico spinal tract as essentially an afferent tract to these centres as did François Frank in 1887, and we might line ourselves with other contemporary critics of the hypothesis of Ferrier and Jackson and hold that there is no more significance in the statement that movements are represented in the cortex than there is in the statement that movements are represented in the skin

But perhaps it might be said this is surely going too far—the evidence of stimulation was only one of the pillars on which the classical hypothesis rested Surely in the first place the consequences of ablation of the precentral gyrus entitle one to think of cortical motor centres

Evidence of Ablation

Let us then consider separately the evidence of ablation of the excitable motor region It could be held until recently that the results of ablation were complementary to those of stimulation, in the sense that there *invariably* followed a loss of the particular movements that stimulation had evoked We now know that the word invariably is not true in a special case

Krynauw (1950) Welch and Penfield (1950) besides ourselves (Bates and McKissock 1951) have all reported that in cases of infantile hemiplegia there may be no further impairment of motor function following removal of a diseased hemisphere which may contain quite a number of motor points giving movement of the opposite diseased limb when stimulated

I would emphasize first that in our material this observation is exceptional—the paresis of the upper limb is usually increased by the operation and complete paralysis may follow in spite of

REFERENCES

BATES J A V (1953a) *Brain* **76** 405
BATES J A V (1953b) *J Physiol* **123** 48P
BATES J A V (1953c) *J Physiol* **123** 4aP
BATES J A V and MCKISSOCK W (1951) *J Physiol* **115** 51P
BURDON SANDERSON J (1874) *Proc Roy Soc* **22** 368
FERRIER D (1886) *The Function of the Brain* Smith and Elder London
FRANCK F (1887) *Leçons sur les Fonctions Motrices du Cerveau* Doin Paris
KRYNAUW R A (1950) *J Neurol Neurosurg Psychiat* **13** 243
LEYTON A S F and SHERRINGTON C S (1917) *Quart J exp Physiol* **11** 135
PENFIELD W (1954) *Brain* **77** 1
PENFIELD W and JASPER H H (1954) *Epilepsy and the Functional Anatomy of the Human Brain* Churchill London
SCHAEFER E A (1900) *Textbook of Physiology* Young and Pentland London
SHERRINGTON C S (1892) *J Physiol* **13** 621
SHERRINGTON C S (1898) *Phil Trans B* **190** 45
SHERRINGTON C S (1906) *The Integrative Action of the Nervous System* Cambridge University Press (2nd edn 1947)
WELCH K and PENFIELD W (1950) *J Neurosurg* **8** 414
WOOD JONES F (1941) *The Principles of Anatomy as seen in the Hand* Bailliere Tindall and Cox London

those very movements that stimulation evoked In so far as the classical hypothesis of the motor system was based on a belief in the complementary nature of the evidence from stimulation and ablation, this is about as direct a refutation of it as one could have At present it is perhaps somewhat beyond the recorded facts of observation, but it is a very important suggestion to explore

Summary and Conclusions

For the past eighty years an hypothesis has been widely accepted as a basis for discussion of the motor system It is held that there are motor centres in the cerebral cortex wherein the most finely differentiated movements are represented and that the activity of these centres is responsible for voluntary movement One of the grounds for this belief is the observation that stimulation of a part of the cortex may produce fine discrete movements But this is not conclusive evidence for the presumed centres for as Sherrington observed, movements of the same class can be produced by sensory stimulation in the bulbo spinal animal, and observations on man indirectly strengthen Sherrington's criticism In the first place, a mechanism which can produce discrete finger movement is developed and in working order in the infant at birth Secondly, cortical stimulation in man characteristically produces movements or changes in posture which resemble those in the general class of superficial reflex movements, movements of spinal automatism or involuntary movements Thirdly fine finger movements identical in character with those produced by cortical stimulation have been produced by stimulation of the internal capsular fibres

A second ground for the classical hypothesis of cortical motor centres is the observation of paralysis which follows ablation of the cortical motor region—and the deduction that cortical stimulation and ablation are therefore complementary techniques in the sense that they are in a peripheral nerve But it is now clear that in other cortical regions their evidence is not complementary and in cases of long standing hemiplegia ablation of an excitable motor region may be followed by no further paralysis In the light of these considerations it would appear that the classical hypothesis is in need of revision

seems to indicate that some form of volume receptor is con cerned in the control of emptying Not only was the intersubject variation small under these conditions but the majority of subjects showed consistent responses from day to day As may

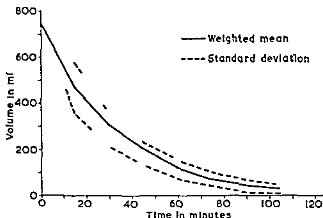


Fig 1 Volume of meal remaining in stomach plotted against time (Hunt and Spurrell 1951)

be seen in Figure 2 the normal emptying pattern is also found in patients with duodenal ulcers The ordinate shows the volume of the test meal in the stomach plotted on a logarithmic scale and the abscissa shows time Each point, which represents the result of a separate test meal on a separate day, falls close to the straight line Hundreds of similar experiments have shown that the stomach usually behaves consistently from day to day under standard conditions This exponential type of emptying pattern was first described by Marbaix in 1898 and has since been confirmed by Salamanca and Picazo (1943) by Hunt and Spurrell (1951) by Hawkins Margolin and Thompson (1953) and by Thornton, Bean and Hodges (1955) It is interesting to note that the relation between the intragastric volume and the gastric output was observed before the somewhat similar rela tionship described for the heart in Starling s Law (1918) The relative outputs of the heart and stomach as pumps may be judged from the fact that the maximal volume entering the

XX

The Investigation of Gastric Digestive Function in Man

J N HUNT

THE purpose of this lecture is to draw attention to some methods of investigating gastric function and to show how the results of such studies may be interpreted with particular reference to patients with duodenal ulcer

Studies of Gastric Emptying

The reliability of measurements of gastric emptying

Under standard conditions the stomachs of different people empty at different rates but the smallness of the variation between subjects under some experimental conditions is remarkable Figure 1 shows the mean emptying pattern in nineteen students for a standard test meal of 750 ml of a solution of pectin and phenol red containing 35 g sucrose/l The ordinate shows the volume of the meal remaining in the stomach, the abscissa shows time These data were obtained by giving 190 standard test meals on different days and recovering the gastric contents after varying intervals of time As two thirds of all the results fell within the area enclosed by the broken lines it is clear that there was little intersubject variation in gastric emptying in these experiments The volume leaving the stomach per minute becomes progressively smaller during the digestive period in such a way that a constant percentage of the volume of the meal in the stomach leaves every minute during the main part of the digestive period An emptying pattern of this kind

inhibit emptying Table 1 lists some of the components of the regulating machinery which must be borne in mind when devising a test to assess maximal gastric emptying power

TABLE 1 A scheme for the regulating mechanism of gastric emptying

Stimulus	*Receptors*	*Effect*
Acid in meal	Precardial	Slows emptying
Increase in volume of meal	Gastric	Hastens emptying
Acid in meal	Postpyloric	Slows emptying
Glucose potassium salts and fat in meal	Postpyloric	Slows emptying
Volume of gastric outflow	Postpyloric	Slows emptying

To find the most suitable volume of meal to use in assessing maximal gastric emptying power studies were made of the relation between the original volumes of a standard test meal containing 35 g sucrose/l and emptying patterns (Hunt and Macdonald 1954) A typical result for one subject is shown in Figure 3 The ordinate shows the rate of emptying in ml per minute, the abscissa shows time Paying attention first to the period 0–10 minutes it may be seen that the larger the meal the greater the initial outflow, 650 ml leaving the stomach in the first 10 minutes with the meal of 1 250 ml For the period between 10 and 40 minutes the rate of outflow of the meal of 750 ml is greater than that for the meal of 1 250 ml At 10 minutes the rate of outflow of the smallest meal of 330 ml is greatest of all, but the smallest meal is technically unsatisfactory because the volume which may be recovered from the stomach after 20 to 30 minutes is sometimes too low to be estimated with precision These points were borne in mind when it was decided to use test meals of 750 ml to study the maximal emptying power of the stomach

Further experiments have shown that meals given down a tube into the stomach empty more rapidly than similar meals swallowed in the ordinary way (Hunt 1956), perhaps because the receptive relaxation of the stomach which results from the movements of swallowing is abolished (Cannon and Lieb,

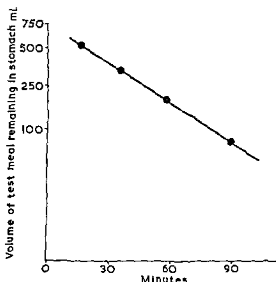


FIG 2 The gastric emptying pattern for 750 ml test meal in a patient *with a duodenal ulcer*

aorta per minute is probably at least a hundred times greater than the maximal volume entering the duodenum per minute

A test of maximal' gastric emptying power

One question about gastric emptying which comes to mind is why does the stomach empty at different rates in different people? One possibility is that the rate of emptying depends simply upon the muscular strength or weakness of the stomach itself, a characteristic which might be a sessed by determining the *maximal* rate at which the stomach can be made to empty

The rate of emptying of the stomach at any moment may be regarded as a result of the interplay of stimulatory and inhibitory influences which together determine how much of the maximal emptying power shall work in driving the gastric contents into the duodenum Thus to assess maximal emptying power by some functional test it is necessary to measure emptying whilst augmenting those influences which stimulate emptying and whilst eliminating as far as possible those stimuli which

maximal rate of emptying in 20 minutes is obtained for solutions of sodium bicarbonate and a slightly slower rate of emptying with solutions of sodium chloride at concentrations of about 120–200 milliosmols per litre On the other hand meals with

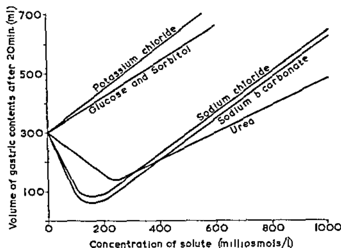


FIG 4 The influence of the concentration of several solutes on the volume of gastric contents 20 minutes after taking a 750 ml test meal

higher and lower concentrations of these solutes operate the duodenal brake so as to give slower rates of emptying as do all solutions of glucose of sorbitol and of potassium chloride It is interesting to note that the relation between the concentration of urea a unionized solute, and the rate of emptying is similar to the corresponding relationship for sodium salts A detailed discussion of these data has been published elsewhere (Hunt 1956) but they can be interpreted as indicating that alimentary receptors with a characteristic permeability and sensitive to osmotic pressure play a part in regulating gastric emptying Of the solutes studied, sodium bicarbonate gives minimal inhibition of emptying but sodium bicarbonate is not as convenient as sodium chloride for inclusion in test meals because it interferes with the simple estimation of the concentration of acid in the gastric contents Thus to determine the maximal gastric emptying power meals of 750 ml of a solution containing 200 milliosmols

1911), or because the stomach is filled more quickly by using the tube

Having decided on the volume of the meal and a way of giving it which will hasten gastric emptying, there remains the

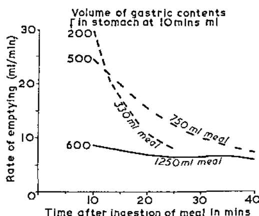


Fig 3 The effect of the volume of meal ingested on the mean rate of emptying of the gastric contents (Hunt and Macdonald 1954)

choice of its composition Although the volume of the meal probably acts on gastric receptors to *stimulate* emptying the chemical constituents of the meal which *inhibit* emptying act very largely on extragastric receptors, which are mainly post pyloric Fat and sugar inhibit emptying and therefore these ingredients ought to be avoided in any test meal designed to study maximal emptying power

To determine the solution which would activate to a minimal extent the postpyloric mechanism which inhibits gastric emptying a systematic study was made of the relation between the concentration of various solutes in test meals and the rate of emptying of the meals The detailed results of a series of experiments in one person are shown in Figure 4 The ordinate gives the volume of the gastric contents remaining 20 minutes after ingestion of the meal and the abscissa gives the concentrations of the various solutes expressed in milliosmols/l of meal so that equal numerical values correspond to equal osmotic pressures It is clear that under the conditions of these experiments a

high osmotic pressure give more reproducible results than these test meals containing 200 milliosmols NaCl/l when the comparison is made in the same person

The rapid emptying of the stomach which is believed to occur more frequently amongst patients with duodenal ulcer than

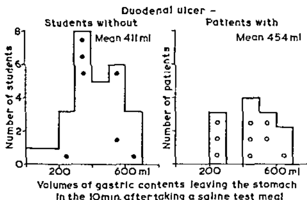


FIG 5 Indices of maximal gastric emptying power

amongst normal persons, might be attributable to such patients having particularly muscular stomachs a peculiarity which could perhaps be detected by comparing their maximal emptying power with that of normal persons Figure 5 also shows data on the volumes of the gastric contents which have left the stomach in the ten minutes after taking the saline test meal for twelve patients with a diagnosis of duodenal ulcer The means and the distribution of the two sets of data are almost identical which suggests that increased maximal emptying power of the stomach is not the cause of any rapid gastric emptying which occurs in patients with duodenal ulcers

The power of the duodenal brake

The rate of emptying of a meal containing a high concentration of glucose for example depends upon a balance between the maximal emptying power and the opposing power of the duodenal brake which is applied as a result of the stimulation of receptors by the osmotic properties of the glucose If the duodenal brake were abnormally weak in patients with duodenal

of sodium chloride per litre have been used In order to make reproducible observations it is desirable that the volume of the gastric contents should be 200 ml or more at the time of the recovery Experience with saline meals has shown that this is achieved by using a digestive period of 10 minutes It must not be inferred that saline entering the duodenum has no inhibitory action on gastric emptying for it has been shown in the dog (Code and Watkinson, 1955) that a solution containing 200 milliosmols NaCl/l injected into the duodenum at rates of about 5 ml /min slows the emptying of a meal of meat It follows therefore that the maximal rate of emptying assessed with a saline test meal could probably be exceeded if it were possible to prevent the gastric effluent from stimulating postpyloric receptors The finding that intragastric instillation of procaine increases the rate of gastric emptying (Roka and Lajtha, 1950) suggests a way in which the inhibitory action of the postpyloric receptors might be still further reduced

Indices of maximal emptying power for normal students and patients with duodenal ulcer

Figure 5 shows in the form of a frequency diagram for twenty seven subjects the calculated values for the volume of gastric contents leaving the stomach in the 10 minutes after taking down a tube a 750 ml test meal containing phenol red as a marker and 200 milliosmols sodium chloride per litre The method of calculation has been published (Hunt 1954a) The volumes leaving the stomach shown on the abscissa vary widely from 55 ml to 660 ml a variation which presumably reflects the different maximal emptying powers in these medical students It is interesting to compare the very wide variation in these findings with the more homogeneous data of Figure 1 obtained when students were given test meals containing 35 g sucrose/l It is clear from these and other data that the composition of test meals can be varied to accentuate or minimize differences between individuals It is generally found that in subjects with high emptying rates a standard stimulus to the duodenal brake is more effective in slowing emptying than it is in subjects with low emptying rates It has also been found that test meals of

responses A solution containing 100 g glucose/l is not a maximal stimulus to the duodenal osmoreceptors but nevertheless it is sufficiently near to such a level to allow the response to be used as a tentative index of the maximal power of the duodenal brake

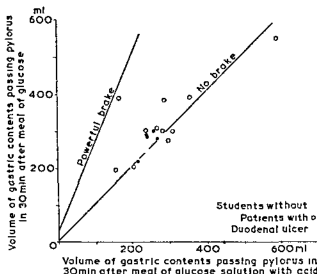


FIG 7 The relation between the emptying of a test meal of glucose solution (100 g /l) and of glucose solution with acid (100 g glucose and 20 m equiv HCl/l)

The threshold of the duodenal brake for hydrochloric acid

The receptors for the duodenal brake are sensitive not only to the osmotic action of glucose but also to the action of hydrochloric acid Because it seemed possible that rapid gastric emptying in patients with duodenal ulcer might result from the insensitivity of the duodenal receptors to low concentration of hydrochloric acid the change in gastric emptying produced by adding 20 m equiv HCl/l of test meal of glucose solution (100 g /l) was investigated The results are shown in Figure 7 for normal students and eleven patients with duodenal ulcer The ordinate gives the values for the volumes of gastric contents leaving the stomach after test meals of glucose and the abscissa

ulcer it might be expected that meals of glucose solution would leave the stomach more quickly in such patients than in normal persons Such an expectation would only be legitimate if the maximal gastric emptying power were the same in the two groups of subjects as Figure 5 showed it to be

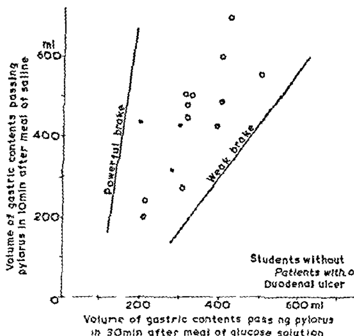


FIG 6 The relation between the emptying of a test meal of glucose solution (100 g /l) and of saline (100 m equiv NaCl/l)

However a more sensitive test of this hypothesis could be made by comparing the volume of the gastric contents leaving the stomach after the saline meal with the volume of the gastric contents leaving the stomach after the meal of glucose solution in each individual This comparison has been made in Figure 6 which shows the volume of the gastric contents leaving the stomach in 10 minutes with the saline meal plotted against the volume of the gastric contents leaving in thirty minutes after the meal of glucose solution It may be seen that the data for the students and for the patients with duodenal ulcers are so intermixed that the two groups cannot be distinguished by their

conclusions can only be accepted with all reserve since they do not take into account the degree of activity of the ulcer, the difference in the ages of the groups or the different degree of physical activity of the two groups at the time of the tests

The use of saline test meals for the investigation of slow gastric emptying

Patients having symptoms associated with very slow gastric emptying are often thought to have some mechanical obstruction to emptying at the pylorus or at the stoma after gastrectomy The diagnosis is usually based on the history and an X ray examination after a barium meal The possibility that such slow emptying may result from a weak gastric musculature or from an unduly active duodenal brake is also worth consideration A patient who had undergone gastrectomy complained of discomfort after eating for some weeks and had a considerable amount of barium in his stomach six hours after a barium meal The surgeon was of the opinion that he had made the stoma too small Nevertheless this subject emptied 400 ml into his duodenum in twenty minutes when he was given a saline test meal and some days later his symptoms disappeared His slow gastric emptying was presumably the result of an over active inhibitory reflex

The influence of the viscosity of a test meal on gastric emptying

It might reasonably be asked whether the study of the emptying of test meals of very low viscosity is relevant to the emptying of ordinary food which gives a more viscous gastric content However a comparison of the emptying of test meals of sugar solution and sugar solution thickened with pectin to give a viscosity comparable to that of a thick motor oil showed that such a change in viscosity had no influence on gastric emptying or secretion (Hunt 1954b)

Studies of Gastric Secretion

The importance of avoiding contamination

When measuring gastric secretory responses it is important to try to avoid contamination by secretions from the duodenum mouth and oesophagus particularly in those instances where the

gives the values for the volumes leaving after test meals of glucose and acid Points which fall high and to the left indicate a *powerful* braking action in response to acid There is no noticeable difference between the two groups in the slowing of gastric emptying produced by the acid

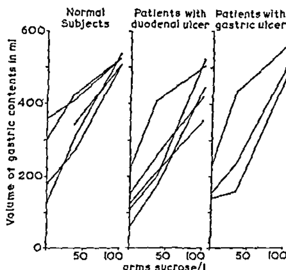


Fig 8 The volume of the gastric contents 30 minutes after taking 750 ml test meals containing 0 35 and 100 g sucrose per litre (Hunt 1954a)

Figure 8 shows the results of similar tests using sucrose to activate the duodenal brake which also failed to show any difference between patients with peptic ulcers and normal students However there was a suggestion in the data that normal persons emptied meals of water less quickly than did the patients with duodenal ulcers (Hunt 1954a)

From the unfinished experiments described above it may be tentatively concluded that the indices of maximal emptying power of the stomach and of the power of the osmotic brake are not noticeably different in a group of patients with the diagnosis of duodenal ulcer from the indices found in a group of medical students There is a suggestion that there may be a difference between the responses of the osmotic receptors of the duodenal brake mechanisms of the two groups for test meals of water which provide a relatively small stimulus to the receptors These

it is clear that the points lie closer to a curved line than to the straight line required by the two component hypothesis It seems unlikely that this divergence from the straight line predicted by the two-component hypothesis can be accounted for

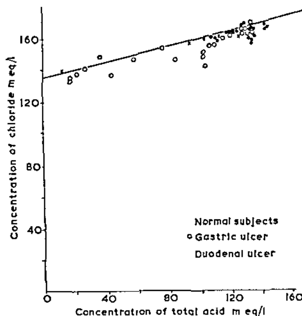


FIG 9 Concentration of total acid plotted against concentration of chloride (Ihre 1938) in gastric secretion

by contamination from extragastric sources for there is a similar divergence in the data of Gudiksen (1950) for feline gastric secretion which was collected without the possibility of contamination This curvilinear relationship between the concentration of acid and chloride in gastric secretion has not received much emphasis before except by Ihre (1938) (see also Heinz and Obrink 1954) possibly because the data which were least open to objection obtained from experiments on dogs with gastric pouches did not cover a sufficiently wide range of acidities to make the curvilinear relationship obvious There is further data at variance with the original two-component hypothesis in some work quoted in Table 3 by kind permission of Dr A Gilman

rate of gastric secretion is low In such circumstances even a small volume of these contaminants, which may all contain bicarbonate on occasion, will significantly alter the composition of the recovered secretions This point makes it desirable to apply powerful excitatory stimuli to the gastric glands whenever this is feasible so as to minimize the effect of contamination from extragastric sources

Variations in the concentration of inorganic ions in gastric secretion

The variations in the concentration of acid and chloride in human gastric secretion collected by Ihre (1938) are shown in Figure 9 As the concentration of acid rises so does the concentration of chloride but to a very much less degree One hypothesis set up by Hollander (1938) to account for these variations postulates that the gastric secretion is a mixture of two parts

TABLE 2 The composition of the hypothetical parietal component and non parietal secretions in man

milliequivalents/l			
Parietal		Non parietal	
H^+ 160	Cl^- 170	Na^+ 160	Cl^- 125
K^+ 10		K^+ 10	HCO_3^- 45
170	170	170	170

The parietal component is thought to issue only from the parietal cells but the non parietal secretions are a mixture of the inorganic external products of all the other types of cell of the gastric mucosa both fundic and antral A composition suggested by Fisher and Hunt (1950) for these two parts for man based on the data of Ihre (1938) is shown in Table 2 Although the non parietal secretions are assumed to have a virtually constant composition this is unlikely to be so under special conditions of stimulation If varying proportions of the two hypothetical components shown in Table 2 are mixed a plot of the concentration of chloride against the concentration of acid in each mixture will lie on the straight line shown in Figure 9 The fit of the experimental points to the line in Figure 9 is an indication of the success of the hypothesis in accounting for the data However

of the amounts of chloride and acid in the secretion The relationship shown in Figure 10 is used to determine the volume of parietal secretion in the data presented later in this lecture

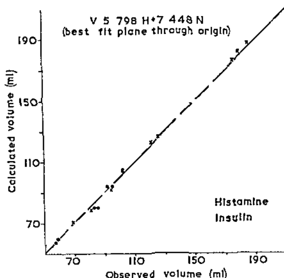


FIG 10 Comparisons of calculated and observed volumes of gastric juice (Fisher and Hunt 1950)

The two component hypothesis has an important consequence A neutral gastric juice is one in which the parietal component is exactly neutralized by the non parietal secretions so that a neutral gastric juice does not correspond to zero parietal activity

The volumes of the hypothetical parietal component and non parietal secretions in a sample of gastric juice can readily be calculated from the amounts of acid and chloride recovered (Hunt 1954a) The data so obtained for the parietal component are probably better indices of parietal activity than the amounts of acid recovered The data for non parietal secretions are to be treated with reserve on theoretical grounds and are sometimes found to be unreliable in practice because they are specially subject to the influence of contamination by extragastric secretions However, provided these reservations are kept in mind the

from his Ph D thesis (1931) It may be seen that at the begin ning of experiments in which the gastric secretion from Heiden hain pouches in dogs was collected there was a considerable rise in the concentration of acid without any change in the concen tration of chloride These data are in harmony with the original Rosemann hypothesis (1907) that the concentration of chloride is constant whilst the concentration of acid varies A modern

TABLE 3 Concentrations of acid and chloride in canine gastric juice (m equiv /l) (Gilman 1931)

Period	Conc H^+	Conc Cl^-
1	125 6	170 4
2	134 0	164 0
3	142 0	164 8
4	142 4	165 2
5	142 0	164 2
1	96 8	162 0
2	121 2	160 0
3	134 0	160 0
4	134 0	160 0

extension of the Rosemann hypothesis is given by Heinz and Obrink (1954) These data which do not fit in with the hypo thesis that the gastric secretion may be considered as a mixture of two components of virtually constant composition have been presented in order that the limitations of the working hypo thesis may be recognized but such divergent data are un common in the literature For the most part the two component hypothesis accounts reasonably well for the relationship be tween the amounts of acid and chloride secreted and the volume of the secretion This may be seen in Figure 10 based on Ihre s data (1938) in which the measured volume of secretion is con trasted with the volume calculated from the amounts of acid and chloride in the secretion by substituting in the relation

Volume = 5 798 (amount of acid)
+7 448 (amount of neutral chloride) expressed in m equiv

Some of the agreement should however be recognized as resulting from the value for volume inevitably appearing in the calculation

component as patients without ulcers The data of Kay from Glasgow (Hunt and Kay, 1954) show a similar difference between the two groups for the diurnal basal secretion of parietal component In our present state of knowledge it is reasonable to assume that in those patients who have such gastric hypersecretion it provides for a duodenal ulcer an unfavourable environment which retards healing and it is therefore a matter of some clinical interest (Atkinson and Henley, 1955) It now remains to frame and test some hypotheses which might account for this hypersecretion under basal conditions

The mechanism of the regulation gastric secretion

The gastric secretory mechanism may be considered to have the three parts of a reflex arc (1) receptors of stimuli which ultimately activate the secretory cells of the mucosa (2) the peripheral effectors, e g the parietal cells and (3) the connexions, either nervous or hormonal, between the receptors and the effectors When there is some quantitative abnormality of secretion the fault may lie in the working of one or several of these three parts Thus one type of analysis of the hypersecretion of patients with duodenal ulcers can be resolved into determining the degrees of reactivity of the receptors and effectors an idea which is illustrated in the following series of figures Figure 11*a* represents the postulated reactivity of these parts of the reflex arc in a normal person A standard stimulus impinges on the receptor which fires one unit of stimulation into the gastric mucosa which forms one unit of secretion Figure 11*b* shows an abnormal arc in which a doubly reactive receptor fires two units of stimulation in response to the standard stimulus so that the secretory response is twice normal In 11*c* the receptor is represented as normally reactive but the doubly reactive mucosa now forms two units of secretion in response to the standard stimulus Figure 11*d* shows a combination of a doubly reactive receptor acting on a doubly reactive secretory mechanism with the resulting 4 units of secretion A normal response from an abnormal mechanism where the doubly reactive receptor operates a half reactive mucosa is shown in Figure 11*e*

concepts of parietal component and non parietal secretions are a convenience in thinking about gastric secretory activity Moreover, when the hypothesis is superseded, data reported in terms of the parietal and non parietal secretions can readily be converted back into amounts of acid and chloride

An Analysis of the Gastric Hypersecretion of Acid by Patients with Duodenal Ulcer

The basal secretion

It is now widely agreed that under basal conditions the diurnal and nocturnal secretion of acid by patients with duodenal ulcer is greater in amount than that of persons without duodenal ulcer

Table 4 The mean volumes of parietal component in the nocturnal secretion of patients with and without duodenal ulcer (Levin Kirsner, Palmer and Butler 1948)

Subjects condition	Number of studies	Mean volume of parietal component (ml)	Standard error of mean
WITHOUT duodenal ulcer	33	240	±22
WITH duodenal ulcer	72	526	±29

The majority of workers who have measured basal secretion have presented their data in terms of the amounts of acid recovered Reasons have been given above for thinking that the amount of acid recovered may not be the best index of the secretory activity of the parietal cells so that in this presentation the data of other workers have been transformed into volumes of parietal secretion which is assumed for the moment to contain 160 m equiv H^+/l and 170 m equiv Cl^-/l (Thompson and Vane 1953) A study of Ihre s data (1938) has shown that these values are applicable to the gastric secretion of patients with peptic ulcers (Hunt, 1951a)

Table 4 shows some data for nocturnal secretion taken from the literature It may be seen that as a group patients with duodenal ulcers secreted more than twice as much parietal

patients with duodenal ulcer secreted about 30 per cent more parietal component than the selected normal persons in response to a body weight dose of histamine (0 1 mgm histamine acid phosphate/10 Kg body weight) If the sole difference between patients with duodenal ulcer and these normal persons lay in the reactivity of the peripheral parietal secretory mechanism it

TABLE 5 Volumes of acid component secreted in response to histamine and insulin (Ihre 1938 Hunt 1950a)

	Normal	Patients with	
		Gastric ulcers	Duodenal ulcers
Number of subjects	18	17	13
Histamine (ml)	91 6	82 4	119 6
Standard error of mean	±7 1	±13 1	±13 1
Insulin (ml)	118 7	102 7	145 8
Standard error of mean	±9 5	±14 7	±17 0

would be expected that the patients would secrete 30 per cent more parietal component than these normal persons in response to any standard stimulus Insulin which stimulates gastric secretion via the vagus as a result of the action of hypoglycaemia on cephalic receptors was also used by Ihre in these two groups of subjects Table 5 also shows that the patients with duodenal ulcer actually secreted 23 per cent more parietal component than the normal persons in response to a standard stimulus with insulin but this figure is not significantly different from the expected 30 per cent Thus these data of Ihre taken at their face value indicate that the hypersecretion of patients with duodenal ulcer in response to insulin can be accounted for by the increased peripheral parietal reactivity demonstrated in the response to histamine

This type of analysis would be more convincing if it were possible to assess the maximal secretory power of the gastric mucosa Thanks to the work of Kay (1953) this is now possible

A test of maximal parietal secretory power

Large doses of histamine are noxious but their effects can be made tolerable by adequate doses of mepyramine maleate

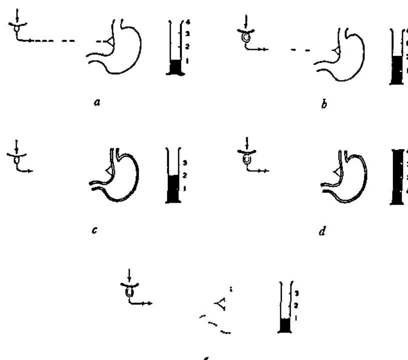


FIG 11*a* A normal arc
b An arc with a doubly reactive receptor
c An arc with a doubly reactive mucosa
d An arc with a doubly reactive receptor and mucosa
e An arc with a doubly reactive receptor and a half reactive mucosa

The assessment of parietal secretory power

The first question to be asked is, Does an abnormally high secretory power of the gastric mucosa account for the hyper secretion of duodenal ulcer? To answer this requires some test which will give an index of parietal secretory power Histamine seems to be a suitable stimulus for use in such a test since it acts on the parietal cell even in a transplanted gastric pouch of gastric mucosa without Auerbach s plexus (Klein, 1932) Table 5 allows a comparison of the secretory responses of selected normal young men with those of male patients with duodenal ulcer based on the data of Ihre (1938) It may be seen that the

patients with duodenal ulcer secreted about 30 per cent more parietal component than the selected normal persons in response to a body weight dose of histamine (0 1 mgm histamine acid phosphate/10 Kg body weight) If the sole difference between patients with duodenal ulcer and these normal persons lay in the reactivity of the peripheral parietal secretory mechanism it

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(Anthisan) which do not block the stimulating action of hista mine on the parietal cells In Kay's augmented histamine test he first collects the basal secretion and then determines the secretory response to a dose of histamine which is known to

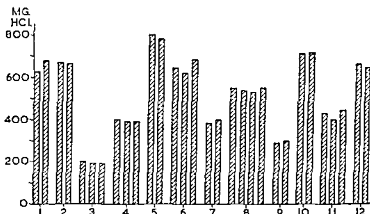


FIG 12 Gastric HCl output after histamine (4 B W doses) Repeated estimations in 12 patients Mgm /30 minutes (Kay 1953)

produce a maximal gastric secretory response in the presence of a protecting dose of mepyramine maleate Figure 12 shows that using this large dose of histamine on several occasions gives very reproducible secretory responses This test was used to assess the 'maximal' secretory power of patients without duodenal ulcer and of patients with duodenal ulcer It may be seen in Table 6 that in the patients with duodenal ulcer, who were candidates for gastrectomy in Glasgow, the mean output of parietal com ponent in 45 minutes after a maximal dose of histamine was 135 ml as compared with 86 ml in the control subjects under *the same conditions There was therefore a significantly in* creased maximal parietal secretory power in these patients with duodenal ulcer These data of Kay probably give a better index of the magnitude of the abnormality in patients with duodenal ulcer than do those of Ihre (1938) because the control subjects of Kay s data were of about the same age and weight as the patients with duodenal ulcer, whereas Ihre s data were for selected young men Thus Figure 11*c* describes more or less

quantitatively the state of the parietal secretory arc in patients with duodenal ulcer The gastric responses to large doses of histamine are maximal for histamine but this does not necessarily mean that no higher rate of secretion is possible However,

TABLE 6 Data on the secretion of parietal component by normal persons and patients with duodenal ulcer (ml /30 min)

	Male normal persons	Male patients with duodenal ulcer		
		No stenosis	Moderate stenosis	Severe stenosis
Number of persons	27	81	42	29
Mean basal secretion of parietal component	15 7	33 8	46 0	39 8
Standard error of mean	±1 7	±2 5	±5 3	±4 6
Mean maximal parietal response to histamine	86 0	135 3	165 1	160 4
Standard error of mean	±9 6	±7 1	±9 7	±10 1
Mean weight (kg)	60 8	58 5	58 0	53 0
Standard error of mean	±1 8	±1 0	±1 1	±1 0
Mean age (years)	44 1	38 3	42 9	49 1
Standard error of mean	±2 5	±1 0	±1 6	±1 4
Mean duration of symptoms (years)	—	13 1	15 0	17 2
Standard error of mean	—	±0 9	±1 3	±1 6

it is difficult to imagine any set of conditions likely to evoke a greater response, for not only is the stimulus to secretion large but by aspirating the secretion the possibility of inhibitory effects operating from the duodenum is minimized

The significance of the dose response relationship for histamine

The hypothesis developed above suggests that a high maximal response to histamine will be associated with a mucosa which will give a high response to any form of stimulus bearing on the parietal cells

It could be objected that patients with duodenal ulcer might have a number of parietal cells with a high threshold for stimulation which would respond to large doses of histamine but not to stimuli of normal physiological quality If this were so the high maximal parietal secretory power in such patients might

(Anthisan) which do not block the stimulating action of hista mine on the parietal cells In Kay's augmented histamine test he first collects the basal secretion and then determines the secretory response to a dose of histamine which is known to

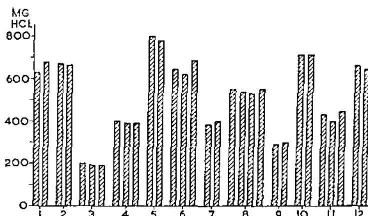


FIG 12 Gastric HCl output after histamine (4 B W doses) *Repeated estimations in 12 patients Mgm /30 minutes (Kay 1953)*

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out of six trials if there were in fact no difference between the two groups in this respect These figures suggest that the increased diurnal basal secretion in patients with duodenal ulcer can be almost wholly accounted for on the assumption that a

TABLE 7 Percentage of the maximal secretory power active in basal secretion

	Male normal persons	Male patients with duodenal ulcer			
		No stenosis	Moderate stenosis	Severe stenosis	All
Mean ratio					
Basal parietal secretion × 100 / Maximal parietal response to histamine	22 4	25 6	26 7	25 4	25 9
Standard error of mean ratio	±2 2	±1 3	±2 0	±2 3	±0 95

normal degree of stimulation is bearing on a peripheral effector of nearly twice the normal power It thus becomes unnecessary to postulate *that the pathways in the vagus mediating the* cephalic phase of secretion are overactive Those who favour this concept of vagal overactivity can point out that the nocturnal basal secretion in patients with duodenal ulcers is much reduced by vagotomy and that the basal secretion must have been the result of activity in vagal secretory fibres Table 8 shows some data derived from a publication by Dragstedt (1952) which allow the volume of parietal component recovered during the night to be calculated It is clear that after vagotomy the recovery fell by about 67 per cent However data from the same group of workers show that the secretory response to histamine fell by 75 per cent after vagotomy Assuming that the change in the response to histamine is proportional to the change in the reactivity of the parietal secretory mechanism the actual fall in the basal output of parietal component was slightly less than would be expected had the stimulus bearing on the parietal cells remained unchanged If it were permissible to follow this argument to its conclusion it would seem that no vagal secretory as distinct from trophic fibres are active in

not account for their high basal secretion of acid However, examination of the relation between the percentage of the maximal secretory power activated by a given dose of histamine in normal persons and patients with duodenal ulcers

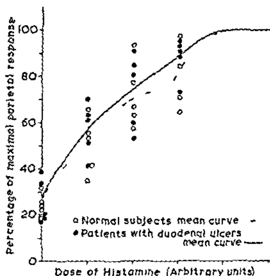


Fig 13 Relation between dose of histamine and parietal response (*Hunt and Kay 1954*)

given in Figure 13 shows that this objection cannot be sustained since the mean curves for five patients without duodenal ulcer and five patients with duodenal ulcer are almost identical

The proportion of the maximal secretory power active under basal conditions

Although the maximal parietal response to histamine may not be the true maximal parietal secretory power the response may be assumed to provide a useful index of the maximum It now becomes possible to ask a new question What percentage of the maximal secretory power is active under basal conditions in patients without duodenal ulcer and patients with duodenal ulcer? *Table 7 shows that 22 per cent of the maximal capacity* is active in normal persons and 26 per cent in patients with duodenal ulcer Such a difference would arise by chance once

found These results can be accounted for by supposing that stenosis will increase gastric distension which is known to be a stimulus to secretion (Hunt and Macdonald 1952, Macdonald and Spurrell, 1953) and that the increased parietal secretory power corresponds to a work hyperplasia of the parietal cells There is some evidence that work hyperplasia can be produced in the stomach for Friedman (1953) found that the weight of the stomach increased in mice when the bulk of their diet was increased by undigestible material, and Cox and Barnes (1945) reported an increase in the number of parietal cells in guinea pigs given injections of histamine in beeswax for three weeks This has been confirmed in dogs by Tongen (1950)

There is evidence which suggests that variation in the parietal responses to standard stimuli amongst normal subjects as well as the difference between the responses of normal subjects and patients with duodenal ulcer can be to a large extent accounted for by the varying parietal secretory power of different normal subjects for the secretory responses to test meals to insulin and to basal conditions are all correlated with the response to histamine (Hunt, 1950b)

The inhibition of gastric secretion

The rate of parietal secretion at any moment depends upon the balance between stimulation and inhibition bearing on the mucosa Quantitative intersubject comparisons of the secretory inhibition produced by standard stimuli are therefore essential for understanding this balance

The two tests which have most convincingly brought out the difference between patients with duodenal ulcer and normal persons were the augmented histamine test of Kay and measurements of basal secretion both of which reflect mainly the increased peripheral reactivity Unpublished studies of the secretory responses to saline test meals at Guy s Hospital show that the parietal secretory response is about twice as great in patients with duodenal ulcer as it is in normal persons The mean amount of acid secreted in response to a 750 ml saline meal of ten minutes duration by a group of twenty seven medical students was 2 6 m equiv (S E of mean $\pm$ 0 3) as compared with

basal secretion in patients with duodenal ulcer had such fibres been active the fall in the output of parietal secretion would have been more than the 75 per cent which can be accounted for on the basis of the reduction in peripheral reactivity as assessed with histamine

TABLE 8 The mean volumes of parietal component secreted in response to basal conditions and in response to histamine before and after vagotomy (*Dragstedt 1952 Oberhelman and Dragstedt 1948*)

Number of patients	Condition	Vol of parietal component (ml) basal secretion per 12 hours	Reduction after vagotomy
135	Duodenal ulcer prevagotomy	514	
70	Duodenal ulcer postvagotomy	170	67%
	Secretion stimulated by histamine		
18	Peptic ulcer prevagotomy	185	
18	Peptic ulcer postvagotomy	47	75%

It seems probable at the moment that the increased 'maximal parietal secretory power found in patients with duodenal ulcers is the result of an increased number of parietal cells in the gastric mucosa of such patients, for Cox (1952) has found that male patients with duodenal ulcer have 75 per cent more parietal cells than male patients without ulcer, whilst Kay's figures show that such patients have a maximal parietal secretory power 72 per cent greater than normal persons The factors which determine the number and reactivity of the parietal cells in the gastric mucosa appear to be of fundamental importance for the understanding of the hypersecretion of parietal component by patients with duodenal ulcer

There are probably a number of influences regulating the parietal secretory power In the analysis of Hunt and Kay (1954) it was found that amongst patients with pyloric stenosis at the time of their gastrectomy the maximal parietal secretory power increased with the duration of the dyspepsia whereas in the other patients without stenosis no such correlation was

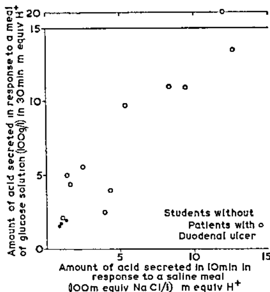


FIG 14 A comparison of the secretory responses to meals of gucose solution (100 g /l) and of saline (100 m equiv NaCl/l)

The inhibition of secretion by the acid in the gastric contents

During the augmented histamine test the whole of the gastric secretion is withdrawn so that there can be no possibility of the secreted acid acting on receptors which might inhibit the gastric secretory response On the other hand when a test meal is used as a stimulus the greater the secretion of acid the more acidic will be the gastric contents and the greater will be the probability of the inhibition of secretion by the action of the gastric contents on duodenal and possibly antral receptors (Woodward Lyon Landor and Dragstedt 1954) Shay (1944) has suggested that the hypersecretion of acid by patients with duodenal ulcer depends upon the failure of the duodenal mechanism to inhibit secretion because its threshold is raised It was therefore decided to determine the response to the addition of acid to a test meal given to normal students and to patients with duodenal ulcer

The choice of the composition of the control test meal in

5 25 m equiv (S E of mean $\pm$ 1 0) secreted by eleven patients with the diagnosis of duodenal ulcer The data are not expressed in terms of parietal component because the meals contained large amounts of chloride which makes the estimation of parietal component less reliable than usual This particular set of data has been chosen because there is presumably a minimal possibility of the inhibition of secretion by the gastric contents acting on duodenal receptors since the meal itself probably has little inhibitory action and in ten minutes the acidity of the gastric contents does not reach levels which are thought to activate the duodenal and possibly the antral receptor mechanisms which inhibit secretion (Woodward, Lyon Landor and Dragstedt, 1954) The same two groups of subjects received 750 ml test meals containing 100 g glucose/l, which left the stomach much more slowly than the saline meal so that a digestive period of thirty minues was practicable The mean responses were 34 4 ml (S E of mean $\pm$3 4) of parietal component for the medical students and 62 ml (S E of mean $\pm$9 8) for the eleven patients with the diagnosis of duodenal ulcer From these data it appears that whether or not the test conditions activate inhibitory receptors the mean total response in these patients with duodenal ulcers is about twice that in normal students a finding which could be accounted for on the basis that such patients have as a group about twice as many parietal cells as these normal subjects

There is a further possibility that if patients with duodenal ulcers have a relatively weak osmotic brake restraining secretion, it might only be detected by a more sensitive test In Figure 14 the amount of acid secreted in response to the saline meal in ten minutes has been plotted against the amount secreted in thirty minutes after the meal of glucose solution The saline meal presumably activates the inhibitory mechanism to a minimal degree whilst the glucose solution is a powerful activator of the mechanism It may be seen in Figure 14 that the points for patients with duodenal ulcer are freely intermixed with those for the medical students so that presumably the osmotic brake on secretion is of about equal power in the patients with duodenal ulcer and the medical students

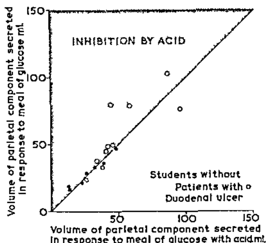


Fig 15 Parietal secretion in 30 minutes after test meal of glucose solution (100 g /l) and glucose solution with acid (100 g /l + 20 m equiv HCl/l)

Conclusion

The possibility that a high gastric secretion in normal persons and in patients with duodenal ulcer may be accounted for by special features in *several* parts of the regulating mechanism is worth consideration The hypersecretion which occurs in some patients with duodenal ulcers could then be regarded as an extension of one end of the normal range rather as patients with high blood pressure of unknown origin may be regarded as providing an extension of the normal range of blood pressure without being in any qualitative way different from persons with lower blood pressures (Miall and Oldham 1955) Such a hypothesis allows for the interaction of hereditary and environmental factors for it is known that very remarkable changes in gastric secretion may accompany change in the circumstances of life (Hunt, 1951b)

SUMMARY

To give a simple probably unduly simple summary of the abnormalities of gastric secretion in patients with duodenal ulcer it may be said that the mean parietal secretory power is

which the acid must be incorporated *is important in interpreting* the results Most stimuli which inhibit gastric secretion simultaneously slow gastric emptying But slowing of gastric emptying gives an increased distension stimulus to the stomach so that the inhibitory action of the meal may be more than counterbalanced *by the increased stimulus to secretion Such a relation*ship between the inhibitory and stimulatory effect of increasing concentrations of sucrose has been found in two normal subjects (Hunt, 1954a) These points were borne in mind when it was decided to use test meals containing 100 g glucose/l and 100 g glucose plus 20 m equiv HCl/l to determine the effect of acid in a test meal on the resulting gastric secretion It was anticipated that the addition of acid to a glucose solution would make little difference to the rate of emptying with the result that the stimulus to secretion would be substantially unchanged

Figure 15 shows on the ordinate the volume of parietal component secreted in response to the meal of glucose solution (100 g /l) and on the abscissa the amount of parietal component secreted in response to a meal of the same solution with 20 m equiv HCl added per litre of meal It is clear that the data for normal persons and patients with duodenal ulcer are freely intermixed and that there is no noticeable difference between the two groups Since there are approximately twice as many points for subjects showing inhibition of parietal secretion as there are for persons showing no inhibition it is clear that 20 m equiv HCl/l is a suprathreshold stimulus for the inhibitory mechanism However in one patient with duodenal ulcer with marked hypersecretion the addition of acid to the meal was followed by an increase in secretion of parietal component

In general the greater is the secretory response of the stomach, the more readily is it inhibited by such a stimulus as high concentrations of sucrose (Hunt Macdonald and Spurrell 1951) The finding that in the two patients mentioned above the addition of 20 m equiv HCl/l of meal failed to inhibit secretion is therefore of some interest It confirms the hypothesis of Shay (1944) with the implication that failure of autoregulation of gastric secretion is a possible cause of hypersecretion but not the sole cause

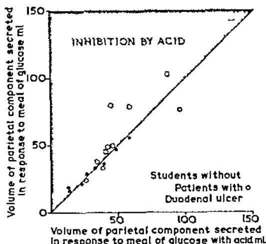


FIG 15 Parietal secretion in 30 minutes after test meal of glucose solution (100 g /l) and glucose solution with acid (100 g /l + 20 m equiv HCl/L)

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The possibility that a high gastric secretion in normal persons and in patients with duodenal ulcer may be accounted for by special features in *several* parts of the regulating mechanism is worth consideration The hypersecretion which occurs in some patients with duodenal ulcers could then be regarded as an extension of one end of the normal range rather as patients with high blood pressure of unknown origin may be regarded as providing an extension of the normal range, of blood pressure without being in any qualitative way different from persons with lower blood pressures (Miall and Oldham 1955) Such a hypothesis allows for the interaction of hereditary and environmental factors for it is known that very remarkable changes in gastric secretion may accompany change in the circumstances of life (Hunt 1951b)

SUMMARY

To give a simple, probably unduly simple summary of the abnormalities of gastric secretion in patients with duodenal ulcer it may be said that the mean parietal secretory power is

about double that of normal persons and this can account for the observed hypersecretion under basal conditions and after stimulation with test meals

In some patients there is in addition a failure of the autoregulation of gastric secretion as shown by Shay

ACKNOWLEDGEMENTS

Much of the work referred to was done with Professor W R Spurrell and Dr I Macdonald at Guy s Hospital and with Mr A Kay F R C S , of Glasgow It is a pleasure to thank many clinical colleagues for permission to investigate their patients with peptic ulcers the patients themselves and the students who have cooperated in these studies

REFERENCES

ATKINSON M and HENLEY K S (1955) *Clin Sci* 14 1
CANNON W B and LIEB C W (1911) *Amer J Physiol* 27 xiii
CODE C F and WATKINSON G (1955) *J Physiol* 130 233
COX A J (1952) *Arch Path Chicago* 54 407
COX A J and BARNES V R (1945) *Proc Soc exp Biol N Y* 60 118
DRAGSTEDT L R (1952) *Rev Gastroenterol* 19 286
FISHER R B and HUNT J N (1950) *J Physiol* 111 138
FRIEDMAN M H F (1953) *J nat Cancer Inst* 13 1035
GILMAN A (1931) Studies in Gastric Secretion Ph D thesis Yale University
GUDIKSEN E (1950) *C R Lab Carlsberg* 27 145
HAWKINS G K MARGOLIN S and THOMPSON J J (1953) *Gastroenterology* 24 193
HEINZ E and OBRINK K J (1954) *Physiol Rev* 34 643
HOLLANDER F (1938) *J biol Chem* 125 161
HUNT J N (1950a) *Lancet* ii 397
HUNT J N (1950b) *Gastroenterology* 16 231
HUNT J N (1951a) *J Physiol* 113 419
HUNT J N (1951b) *J Physiol* 113 169
HUNT J N (1954a) *Guy s Hosp Rep* 103 161
HUNT J N (1954b) *Lancet* i 17
HUNT J N (1956) *J Physiol* 132 267
HUNT J N and KAY A W (1954) *Brit med J* ii 1444
HUNT J N and MACDONALD I (1952) *J Physiol* 117 289
HUNT J N and MACDONALD I (1954) *J Physiol* 126 459
HUNT J N MACDONALD I and SPURRELL W R (1951) *J Physiol* 115 185

HUNT J N and SPURRELL W R (1951) *J Physiol* **113** 157
IHRE B (1938) *Acta med scand* Supp 95
KAY A W (1953) *Brit med J* **ii** 77
KLEIN E (1932) *Arch Surg* **25** 442
LEVIN E KIRSNER J B PALMER W L and BUTLER C (1948) *Arch Surg* **56** 345
MACDONALD I and SPURRELL W R (1953) *J Physiol* **119** 259
MARBAIX O (1898) *Cellule* **14** 249
MIALL W E and OLDHAM P O (1955) *Clin Sci* **14** 459
OBERHELMAN H A and DRAGSTEDT L R (1948) *Proc Soc exper Biol Med N Y* **67** 336
ROKA C and LAJTHA L G (1950) *Brit med J* **i** 1174
ROSEMANN R (1907) *Pflug Arch ges Physiol* **118** 467
SALAMANCA F E and PICAZO J (1943) *Trab Inst nac Cienc méd Madr* **1** 3
SHAY H (1944) *Bull N Y Acad Med* **20** 264
STARLING E H (1918) Linacre Lecture The Law of the Heart London
THOMPSON J E and VANE J R (1953) *J Physiol* **121** 433
THORNTON G H M BEAN W B and HODGES R E (1955) *J clin Invest* **34** 1085
TONGEN L A (1950) *Surgery* **28** 1009
WOODWARD E R LYON E S LANDOR J and DRAGSTEDT L R (1954) *Gastroenterology* **27** 766

XXI

The Treatment of Hepatic Coma

J F STOKES

HEPATIC coma is not a common condition and is capable of unpredictable and spontaneous recovery, these two facts make it extremely difficult to judge the effect of treatment and give rise to contradictory and confusing reports The position is still worsened by lack of precision in the definition of hepatic coma' various kinds of coma plus jaundice or coma plus enlarged liver may be collected together in an attempt to provide a series of cases on which the effects of treatment may be judged, and the fact that severe electrolyte disturbance and cerebral manifestations of thiamine deficiency are not uncommon in cirrhotics may be overlooked Recently too, the clinical pattern of illness produced by viral infection has become less clear cut this influences the problem in that coma due to encephalomyelitis may be present together with clinical and biochemical evidence of impaired liver function Comparison between series is further complicated by the fact that hepatic coma is notoriously more difficult to influence when it occurs in association with acute liver disease than with cirrhosis

The forty five cases Miller and I reported in 1947 (Stokes and Miller 1947) were all in coma as a result of acute hepatitis caused by a particularly virulent virus All but one of these died but they cannot be used as a yardstick by which to measure the progress we have made in treatment since any current series is likely to include a high proportion of comatose cirrhotics, in whose state as we shall see certain temporary modifications can be made

Though hepatic coma seems at first sight an unpromising

subject to discuss here, there is no doubt that our understanding of the condition has increased in the last decade and, encouraged by the belief that these lectures are designed to provoke rather than instruct, I want to use this opportunity to see what can be learned from forty seven cases of hepatic coma which were observed at University College Hospital or in my private practice between 1948 and 1955 The material from which I am arguing is shown in Tables 1 and 2

TABLE 1 Hepatic coma 1948-55

	Cases	Died	Recovered
Acute hepatitis	8	8	0
Subacute hepatitis	8	8	0
Cirrhosis	31	28	3

TABLE 2 Cirrhosis in hepatic coma 1948-55

	Cases	Died	Recovered
Alcoholic	11	10	1
Cause obscure	10	9	1
Post hepatitic	6	5	1
Ulcerative colitis	2	2	0
Biliary	1	1	0
Haemochromatosis	1	1	0

It will be seen that we have had no striking success in saving these people s lives but I should say that among the group of thirty one cirrhotics we can add nine episodes of coma occurring in eight patients between one and twenty two months before death, making a total of twelve attacks of coma followed by recovery either spontaneous or consequential to treatment I would emphasize that these all occurred in cirrhotic patients and were preceded by gastro intestinal haemorrhage in four instances No case of acute hepatitis survived coma

The position in regard to treatment at the beginning of this series of cases was that I was convinced of two things in the light of experience of hepatic coma in Burma Firstly, I was convinced of the danger of giving normal doses of morphine or barbiturates to patients in the active and sometimes violent phase of coma liver failure allows of the continued action of

these drugs which remain unchanged in the body tissues and may tip the balance against the patient by prolonging coma and depressing respiration Paraldehyde is the only safe drug to use if the violence of coma interferes with treatment Secondly, I was convinced of the value of parenteral vitamin K, which might limit haemorrhage not only into the gut but also into the liver itself and so prevent further hepatocellular damage, gastro-intestinal haemorrhage is, as we shall see, of importance in the comatose cirrhotic, while bleeding into the liver is of greater consequence in cases of fulminant hepatitis

PROTEIN AND AMMONIA

The value of protein treatment, however, seemed to be questionable Enthusiasm derived from occasional Sunday morning feeding of Himsworth s rats was modified by awareness of the syndrome of meat intoxication in dogs I feel sure in retrospect, that uncertainty on this point brought about the deaths of two of my patients who were fed protein vigorously as soon as they emerged from coma and had to lapse back into unconsciousness before they could escape the deleterious effects of treatment

The present position of protein in the therapy of hepatic coma is clear It must be avoided The forced feeding of meat to dogs with an Eck fistula has been known since 1893 (Hahn Massen, Nencki and Pavlov) to produce neurological damage, and varying explanations have been offered to account for this (Magnus Alsleben, 1920, Fuchs 1921 Svec and Freeman 1949) Burchi in 1927 observed high blood ammonia levels in cirrhosis and van Caulaert and Deviller (1932) and Fuld (1933) found that ammonium salts were capable of producing coma and high blood levels in cirrhotics Here the matter rested until 1952 when interest was reawakened by Phillips Schwarz, Gabuzda and Davidson reporting the production of hepatic coma in cirrhotics by feeding various nitrogenous substances Since then different degrees of neurological disorder from full coma through episodic stupor to spasticity and tremor have been repeatedly brought about in some cirrhotics by feeding high protein diets by giving ammonium salts or ion exchange resins in the ammonium phase (Gabuzda Phillips and Davidson, 1952)

These findings have been confirmed in this series They provide difficulties in treating ascitic and diabetic patients These can be overcome easily in the former by avoiding ammonium containing medicines but the adjustment of the protein carbohydrate balance of the diet in haemochromatosis is awkward on account of the insulin resistance so often encountered

These neurological changes have been correlated with high levels of ammonia in the systemic blood (Riddell, Kopple and McDermott 1954 McDermott, Adams and Riddell 1955), and the view that these levels are achieved by direct access of ammonia from the gut to the systemic veins via a network of venous collateral channels developed in response to portal hypertension (Sherlock, Summerskill, White and Phear, 1954) receives support from two observations, first the appearance of coma and increase in blood ammonia as a result of porta caval shunt operations and second the demonstration of high blood ammonia levels in cirrhotics whose liver function is reasonably good

There is a paucity of observations on ammonia levels in acute hepatitis Kirk (1936) reports them as normal, but he was not dealing with comatose cases and one of Riddell and McDermott s (1954) cases in coma as a result of acute hepatitis, had a distinctly high level and this can only have been the result of hepatocellular failure

There is however a certain lack of correlation between blood ammonia levels and coma in some cases (Singh, Barclay and Cooke 1954) Though most patients in coma will usually show a high reading Summerskill (1955) found two out of twenty nine cases with normal levels and Eiseman (discussing McDermott, Adams and Riddell 1954) found normal levels in about half his cases of hepatic coma

Consciousness may be maintained too in the face of blood ammonia levels which in another person would be associated with deep coma in this context however it is difficult to avoid comparison with uraemia in which the level of consciousness depends more on the speed of accumulation of urea in the blood than on the absolute reading

Those who are familiar with the recent vicissitudes of Professor Quatermass s associates will have realized the popular

appeal of ammonia as a substance capable of producing neuropsychological disorder, and the ammonia story as a whole carries some conviction, though I do not think it can provide a complete explanation of hepatic coma It bears on treatment not only in the prophylaxis of coma by giving a low protein diet and avoiding ammonium containing medicines in patients with a dangerously low reserve of liver function, but also in the treatment of established coma when this has been precipitated by gastro intestinal haemorrhage This, of course, only occurs in cirrhotics, as opposed to patients with acute hepatitis, and in this series haemorrhage shortly preceded coma in nineteen instances in the thirty-one cirrhotics

Haemorrhage

I want to bring out three points in relation to haemorrhage in cirrhosis Figure 1 shows the interval elapsing between haemorrhage and the onset of coma As can be seen, we have less than 48 hours in most cases in which to take effective prophylactic action against coma

The next two figures show the interval in time between the onset of haemorrhage and death I have had to separate Figure 2, which comprises cases who have survived haemorrhage for many months from Figure 3, constructed from those who died shortly after haemorrhage for the sake of clarity Figure 2 shows that many of these cirrhotics sustained substantial bleeding from oesophageal varices up to a surprisingly short time before death without showing abnormal neurological signs It shows that gastro intestinal haemorrhage is not so dangerous if liver function is not too far impaired But it is possible that repeated or prolonged bleeding progressively reduces hepatic function in these cases and we must not neglect this aspect of the effects of haemorrhage

It is not uncommon to find a cirrhotic surviving a run of haemorrhages over a year or two and succumbing to a final bleed which is the first one to be followed by coma It is worth while recalling that Rappaport, Borowy and Lotto (1952) concluded that hepatic anoxia was the basis of the experimental ischaemic coma they induced in dogs

Figure 3 shows that once haemorrhage has produced coma, the prognosis is grave Though haemorrhage and its effects eventually overcame these patients, death occurred more com monly from coma than from exsanguination In addition to

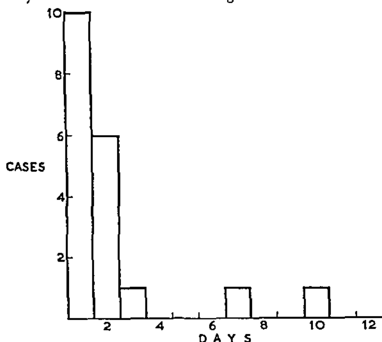


FIG 1 Interval between occurrence of haemorrhage and onset of coma in nineteen cirrhotics

transfusion therefore it is rational to empty the gut of blood as far as possible after a haemorrhage Colonic washouts are harmless enough and purgation may be tolerated even by patients as ill as these but emptying the stomach entails passing a tube past the bleeding point and this may aggravate the haemorrhage The Sengstaken tube has been devised to stop bleeding by compression of oesophageal and gastric varices between inflated bags but it is difficult to handle in semi comatose patients and its advantages when in position may be outweighed by the increase in blood loss attendant on its effective passage Oral thrombin has been recommended for the

control of oesophageal oozing (Daly, 1947) but, in my experience, has not been helpful

The capacity of haemorrhage from oesophageal varices to *initiate coma* and the usual *fatality of the coma when it occurs*

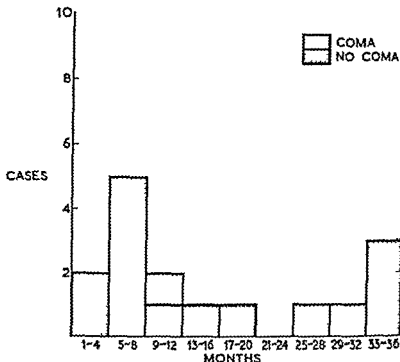


FIG 2 Interval between haemorrhage and death in sixteen cirrhotics

underline the importance of prophylactic measures against recurrent bleeding Shunt operations which involve the opening up of large *new portal systemic channels are not wholly to the* advantage of the patient since they increase the dangers of what Sherlock has called portal systemic encephalopathy The ideal operation for the prevention of *bleeding should obliterate* established oesophageal varices without opening up new anas*tomoses* The injection of varicosities by sclerosing fluids as suggested by Crafoord and Frencker (1939) and as carried out by Macbeth (1955) or better still, direct ligation of submucosal

veins as practised by Phemister and Humphreys (1947), Allison (1950) and Wooller (1955) both come near to satisfying these requirements and are rational manœuvres even if their temporary effect implies the need for repeated surgical attacks The

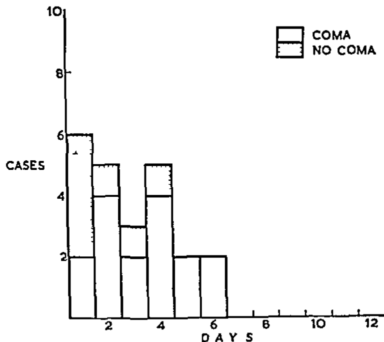


FIG 3 Interval between haemorrhage and death in twenty three cirrhotics

portal pressure is unaffected or even raised by these procedures but the theoretical fear of precipitating or increasing ascites does not seem to be justified by events and, as is well known many other factors are more important in determining the retention of fluid in the peritoneal cavity

GLUTAMIC ACID

The other way in which the ammonia story bears on the treatment of hepatic coma is in its metabolic relations with glutamic acid Krebs (1935) in a discussion of the metabolism of amino acids states that glutamine can be synthesized from ammonia

and glutamic acid fairly fast in the presence of plenty of carbo hydrate by animal brain slices, Weil Malherbe (1950) is of the opinion that glutamic acid plays a prominent role in an enzyme system designed for the removal of intracellular ammonia

Walshe (1951), in discussing the pathogenesis of hepatic coma, suggests that glutamic acid metabolism in the brain may be interfered with, and the ammonia binding action of glutamic acid impaired He also supposes that the reaction glutamic acid ⇌ alpha ketoglutaric acid ⇌ pyruvic acid may be upset, and it may be significant that both these latter substances are known to be found in the blood in excess in hepatic coma (Watson, 1950, Neefe, 1950, Amatuzio and Nesbitt, 1950, and Butt, 1954) The precise meaning of these changes is not clear, but it would appear that the citric acid cycle is upset in some way (Bessman, Fazekos and Bessman, 1954) and Walshe's suggestion that glutamic acid might at least improve the ammonia binding mechanism in the brain seems a reasonable one

There is general agreement, however, that the results of treatment of coma in acute hepatitis with this substance are disappointing Walshe himself (1955) now subscribes to this view Three patients in hepatic coma resulting from acute hepatitis in this series received glutamic acid and derived no benefit from it

Its effect in cirrhotics can only be properly assessed in those cases who have gone into coma without a preceding haemorrhage or in whose cases no active steps have been taken to remove blood from the gut which in itself might be enough to lighten coma These criteria are only satisfied by thirteen cases in this series In these there was definite improvement in eight, no effect in three and doubtful benefit in two Seven out of the eight who improved subsequently died within a week or two and glutamic acid failed to control their final coma the survivor is still enjoying a normal level of consciousness one year after recovery These figures suggest that there is a case to be made out for giving glutamic acid to comatose cirrhotics even though the benefit it may confer is only likely to be temporary and it is evidently not the answer to the whole metabolic disturbance present

FOETOR HEPATIS

When we look around for consistent metabolic features of hepatic coma other than raised blood ammonia levels we can not fail to be struck by hepatic foetor Recently Challenger and Walshe (1955a) have isolated methyl mercaptan from the urine of a patient with marked oral and urinary foetor, and they believe that foetor hepatis is caused by elimination from the body of this substance dimethyl sulphide or dimethyl disulphide both of which might be formed in the body from methyl mercaptan The pharmacology of methyl mercaptan, CH_3SH, is little known but Challenger and Walshe (1955b) suggest that it may be toxic by virtue of its close structural relationship to hydrogen sulphide, HSH, and to methyl alcohol CH_3OH They postulate methionine as a possible source of mercaptan and note the accumulation of methionine in the blood in hepatic coma due to failure of transmethylation functions of the liver But mercaptans are known to be present in the gut and it seems possible that they might accumulate in the same way as ammonia I mention this because I have at times wondered whether foetor is more often present in the coma of acute hepatitis as opposed to that of cirrhosis and that it might indicate the presence of a product of autolysis of liver cells rather than an accumulation of a breakdown product from the gut In trying to decide this point in retrospect I do not find my Burmese records particularly helpful, in the Orient one s olfactory apparatus is mercifully subject to the physiological principle of fatigue and I can draw no conclusions The facts that foetor is not present in cases of cirrhosis in normal consciousness, even in the face of a big collateral circulation and the persistence of foetor in patients who have received nothing by mouth for as long as ten days argue that it might be associated with hepato cellular autolysis But in this series foetor was noted in roughly equal proportions in the two groups four out of eight in acute hepatitis and thirteen out of thirty one in cirrhotics It is striking that clinically identical states of coma may be found in association with livers whose histology varies between the wide spread destruction and lack of recognizable liver tissue so characteristic of acute fulminant hepatitis and the regeneration

nodules of the cirrhotic, in which the liver cells are surprisingly well preserved It does not seem reasonable to blame products of their autolysis for foetor or for coma

Experiments on mice at the Toxicology Research Unit carried out by Dr Barnes (Walshe, personal communication) suggest that methyl mercaptan might be concerned in the production of unconsciousness in man in the concentrations reasonably anticipated in hepatic coma, but that dimethyl sulphide and dimethyl disulphide can be exculpated in this context The importance of sulphur metabolism in the production of coma is not yet clear, but its consideration has not so far resulted in any therapeutic advance

TABLE 3 Composition of faeces

Water
Endogenous fat
Mucus
Epithelial cells
Digestive enzymes
Bile steroids
Inorganic salts of Ca Mg Fe Cu
Micro-organisms
Acetic lactic butyric and other organic acids from CHO fermentation
Tyramine histamine cadaverine and putrescine by bacterial decarboxylation of amino acids
Indole and skatole by partial degradation of tryptophane
H_2S CO_2 CH_4 H_2 NH_3 phenols and mercaptans all by bacterial action

In my view the answer to hepatic coma lies in the gut We have to remember that stools of a sort are passed even by starving patients and Table 3 will remind you of their composition

Somewhere in this list it seems we should find something significant Cooke (1955) for instance finds that certain indoles are present in increased quantities in the stools of patients suffering from idiopathic steatorrhoea in two cases he noticed neurological signs similar to those found in hepatic coma and in one of these cases no liver damage was demonstrated

It will be observed that bacteria are at work in the production of many of these substances Members of the tetracycline group of antibiotics have been recommended in the treatment of

hepatic coma in the hope of suppressing or altering some of the metabolic processes carried out in the intestine These drugs have not been given consistently in this series and I cannot comment on their usefulness We should remember that the tetracyclines can produce troublesome diarrhoea and this may aggravate the low serum potassium which is not infrequently present in hepatic coma

Mention must be made here of the views of Gould (1954, 1955) who claims that high dosage intravenous medication with mixed vitamins might be expected to influence hepatic coma, as well as many other states of impaired consciousness, by improving the intracellular metabolism in the brain Though I believe that this treatment is of benefit to confused alcoholics, I have no experience of it in hepatic coma

Glucose

Brain cells require not only oxygen but glucose, and it seems reasonable to give large quantities of glucose to patients in hepatic coma not only to help to form the glycogen necessary for the proper reconstruction of liver tissue (Jones, 1936 Foulk, Butt, Stauffer Baggenstoss and Gross 1955) but also to help brain cells carry out their normal metabolic processes including the binding of ammonia

At the same time glucose will reduce endogenous protein breakdown which in itself may throw further work on the liver Schoenheimer (1942) has studied the fate of amino acids in the liver with the aid of heavy nitrogen and deuterium and has shown that they may follow at least four separate lines of intrahepatic metabolism all of which involve energy Any manœuvre which reduces the amino acid level in the blood is justified by this argument alone apart from any possible toxic effects of raised blood amino acids on the brain It has been suggested too (Rappaport 1951) that the infusion of a hypertonic solution might be helpful in reducing the cerebral oedema sometimes found in hepatic coma There is no evidence that hypoglycaemia is responsible for any fraction of naturally occurring coma though it may be relevant to some aspects of experimentally produced coma in animals Indeed the full

picture of hepatic coma may be seen in haemochromatosis or cirrhotics with incidental diabetes with blood sugar levels as high as 300 mgm per cent, as occurred on three occasions in this series Nevertheless, glucose remains the one food which can be given to these patients with impunity and is the cornerstone of treatment Bollman's (1949) observation that dogs given enough intravenous glucose to keep the blood sugar level between 200 and 300 mgm per cent for 36 hours produced definite bilirubinaemia and marked dye retention in the liver seems to have no counterpart in human medicine

Since glucose may have to be given parenterally for many days it is wise to give a concentrated 20 per cent solution so as to avoid iatrogenic electrolyte disturbances of which the most probable is overdosage with water Sodium deficiency is not likely to occur in diffuse liver disease in the absence of ascites, but the presence of hypokalaemia has been stressed by Artman and Wise (1953) This demands the close watch on urinary output and state of serum electrolytes that is accorded to any patient unable to take food orally It may be necessary to give potassium supplements There is a certain danger in giving potassium into an intravenous drip if the fluid is being delivered into a vein close to the heart

If we give 20 per cent glucose solution into a superficial vein the chances of its thrombosing are high clots are likely to form even in the face of such factors as hypoprothrombinaemia and thrombocytopaenia which may be present, in this sense to advantage, in liver failure

So far, we have got round this difficulty by passing a polythene tube and delivering glucose into a large vein, either the inferior vena cava or one of the innominate veins This technique needs a certain amount of practice and the tube has become occluded by clot sometimes even when in the correct position Furthermore it carries the risk of inducing hyperkalaemia if potassium supplements are being given unless extremely close watch is kept on the rate of infusion

Patients on systemic cortisone treatment for any reason are thought to have a low incidence of phlebitis after intravenous infusions This is presumably due to the capacity of cortisone

to suppress inflammatory reaction This has led us to a trial of hydrocortisone added to the infused fluid given by ordinary needle into a superficial vein, in an attempt to circumvent the difficulties of infusion by polythene tube to which I have just referred We have used 10 mgm hydrocortisone per litre of 20 per cent glucose The early results have been encouraging in *that our last three cases of hepatic coma treated in this way have* failed to show any macroscopic or microscopic evidence of venous thrombosis or inflammation when autopsy studies, as usual, became available Dr Polak whose idea this was, is publishing details of these cases as a preliminary communication and a larger scale trial of the method is under way

Further Lines of Investigation

Before I finish, I would like to take a look at the possible angles from which further knowledge of hepatic coma may be gained, as this is an essential prelude to any advance in treatment

If we consider first what type of case to study, it is necessary to clarify what we mean by hepatic coma It is important to exclude cases who may be in coma as a result of gross electrolyte disturbance or the effect of alcohol either direct or through conditioned vitamin deficiency These factors are likely to operate in cirrhotics, and must be carefully assessed In practice we have to study cirrhotics, since cirrhosis is so much commoner than fulminant viral hepatitis

It is interesting to speculate, for instance, how far alcohol may have influenced the histological findings in the brains of the patients examined by Adams and Foley (1953) Nearly all the cases they studied were cirrhotics, cirrhotics in America are nearly all alcoholic and the proportion of ethyl alcohol consumed is probably lower than in this country This gives us a better chance of getting the answer here where we have a higher proportion of post hepatitic cirrhosis or cirrhosis of obscure aetiology than in the United States and our alcoholic cirrhosis is more purely ethylic

It seems, too, that we might advance by studying those cases of steatorrhoea in which some of the neurological accompaniments of hepatic coma have been observed It is possible that

investigation of substances such as indoles, which are known to be present in the gut, and which may be found in excess in the urine of patients with steatorrhoea (Aterman, Boscott and Cooke, 1953), may provide a clue as to what fractions of protein breakdown other than ammonia play a part in the production of coma

Cooke (1955) also calls attention to the frequency of tremor and confusion in the anoxia of cor pulmonale These cases do not show the pyramidal signs which occur so commonly in hepatic coma (Stokes, Owen and Holmes, 1945) and I do not think they help us much in this context, but they do raise the question as to whether the tremor seen in liver failure is as typical as has been made out I have serious doubts on this point and I think it is a pity that the term 'flap, previously evocative of nothing more significant than the activities of the third of W S Gilbert's three kings of Chikeraboo should now have acquired a specific hepatic connotation The tremor may indicate no more than the effects of anoxia in brain cells

Coma must ultimately depend on interference with neurones but I doubt whether deeper neuro histological studies will result in any dramatic advance in therapy It is only recently that any remarkable changes have been found In 1952 Adams and Foley, using special methods not easily adapted to routine histological practice showed swollen and proliferated astro cytes chiefly centred on the basal ganglia, and occurring most strikingly in the coma of cirrhosis as opposed to the coma of acute hepatitis Astrocytes are feeding cells and this suggests that a breakdown of some enzyme system may prevent neurones from accepting food from them so that they swell Whatever toxic metabolites produce coma they are, of course more likely to be accumulated in the blood over a long period of time in cirrhotic cases and these histological changes may be no more than a reflection of the progressive inability of neurones to accept from their donor astrocytes something necessary for their internal metabolism

Whatever you may think of the ethics of direct intraven tricular injection of substances in man there is no doubt that Feldberg and Sherwood (1954a b) have produced some

interesting results with the technique they have devised, and they recognize distinct behaviour patterns in animals in response to the intraventricular injection of individual drugs They find a basic pattern of retching vomiting salivation and tachypnoea which is independent of what substance is injected

In addition however, acetyl choline gives rise to stupor, adrenaline results in a state resembling light sodium pento barbitone anaesthesia, decamethonium produces twitching and spasticity while banthine results in motor incoordination This line of attack opens up a new avenue for the investigation of metabolic disturbances affecting brain tissue such as we are discussing today

It may be that a combination of careful screening of intestinal contents and direct application of component substances to brain tissue through a cannula tied into a lateral ventricle will in time tell us why patients die as a result of severe diffuse liver disease and so allow of a more rational plan of treatment

In the meanwhile we should not stray too far along the road to therapeutic nihilism An awareness of the nature of the dangers of haemorrhage and a willingness to use a harmless substance such as glutamic acid may prolong the life of the cirrhotic, provided that the iatrogenic hazards of morphine poisoning and electrolyte imbalance are avoided And sufficient glucose, given in concentrated form either by polythene tube or in combination with hydrocortisone into a superficial vein may serve to keep the sufferer from acute hepatitis afloat until nature throws one of her rare and unpredictable lifebelts to the liver cells

ACKNOWLEDGEMENTS

I wish to thank my colleagues at University College Hospital who have allowed me access to the records of those cases who were not under my care

REFERENCES

ADAMS R D and FOLEY J M (1953) *Ass Res Nerv Ment Dis Proc* 32 198

ALLISON P R (1950) *Ann Surg* 132 808

AMATUZIO D S and NESBITT S (1950) *J clin Invest* 29 1486

Artman E L and Wise R A (1953) *Amer J Med* 15 459
Aterman K Boscott R J and Cooke W T (1953) *Scand J clin lab Invest* 5 3
Bessman S P Fazekos J F and Bessman A N (1954) *Proc Soc exp biol Med* 85 66
Bollman J L (1949) *Macy Foundation Rep* p 117
Burchi R (1927) *Kongr inn Med* 47 80
Butt H R (1954) *Arch int Med* 94 331
Challenger F and Walshe J M (1955a) *Biochem J* 59 372
Challenger F and Walshe J M (1955b) *Lancet* i 1239
Cooke W T (1955) *Proc roy Soc Med* 48 484
Crafoord C and Frencker P (1939) *Acta otolaryngol* 27 4 2
Daly B M (1947) *Amer J Surg* 55 238
Eiseman B (1954) Discussion on McDermott *et al* *Ann Surg* 140 539
Feldberg, W and Sherwood S L (1954a) *J Physiol* 123 148
Feldberg W and Sherwood S L (1954b) *J Physiol* 125 488
Foulk W T Butt H R Stauffer M H Baggenstoss A H and Gross J B (1955) *Gastroenterology* 29 171
Fuchs A (1921) *Wien med Wchnschr* 71 710
Fuld H (1933) *Klin Wchnschr* 12 1364
Gabuzda G J Phillips G B and Davidson C S (1952) *New England J Med* 246 124
Gould J (1954) *Proc roy Soc Med* 47 215
Gould J (1955) *Proc roy Soc Med* 48 487
Hahn M Massen O Nencki M and Pavlov J (1893) *Arch exper Path u Pharmacol* 32 161
Jones C M (1936) *Am J digest Dis* 3 624
Kirk E (1936) *Acta med scandinav* Suppl 77 p 74
Krebs H A (1935) *Biochem J* 29 1951
Macbeth R G (1955) *Brit med J* ii 877
Magnus Alsleben E (1920) *Ergebn d Physiol* 18 52
McDermott W V Jr Adams R D and Riddell A G (1954) *Ann Surg* 140 539
McDermott W V Jr Adams R D and Riddell A G (1955) *Proc Soc exp biol med* 88 380
Neefe J R (1950) *Macy Foundation Rep* p 61
Phemister D B and Humphreys E M (1947) *Ann Surg* 126 397
Phillips G B Schwarz R Gabuzda G R and Davidson C S (1952) *New England J Med* 247 239
Polak A In the press
Rappaport A M (1951) *Macy Foundation Rep* p 161
Rappaport A M Borowy Z J and Lotto W N (1952) *S Forum* p 504
Riddell A G Kopple P N and McDermott W V Jr (1954) *Surgery* 36 675

RIDDELL A. G and MCDERMOTT W V, Jr (1954) *Lancet* i 1263
SCHOENHEIMER R (1942) *The Dynamic State of Body Constituents* Harvard University Press Cambridge Mass
SHERLOCK S SUMMERSKILL W H J WHITE L P and PHEAR E A. (1954) *Lancet* ii 453
SINGH I D BARCLAY J A. and COOKE W T (1954) *Lancet* i 1004
STOKES J F and MILLER A. A (1947) *Quart J Med* 16 211
STOKES J F OWEN J R and HOLMES E G (1945) *Brit med J* ii 642
SUMMERSKILL W J H (1955) *Proc roy Soc Med* 48 482
SVEC M H and FREEMAN S (1949) *Amer J Physiol* 159 357
VAN CAULAERT C and DEVILLER C (1932) *C R Soc Biol Paris* 111 50
WALSHE J M (1951) *Quart J Med* N S 20 420
WALSHE J M (1955) *Lancet* i 1235
WATSON C J (1950) *Macy Foundation Rep* p 61
WEIL MALHERBE, J (1950) *Physiol Rev* 30 549
WOOLLER G (1955) *Proc roy Soc Med* 48 486

ARTMAN, E L and WISE R A (1953) *Amer J Med* **15** 450
ATERMAN, K, BOSCOTT R J and COOKE W T (1953) *Scand J clin lab Invest* **5** 3
BESSMAN, S P FAZEKOS J F and BESSMAN A N (1954) *Proc Soc exp biol Med* **85** 66
BOLLMAN J L (1949) *Macy Foundation Rep* p 117
BURCHI R (1927) *Kongr inn Med* **47** 80
BUTT, H R (1954) *Arch int Med* **94** 331
CHALLENGER F and WALSHE, J M (1955a) *Biochem J* **59** 372
CHALLENGER, F and WALSHE J M (1955b) *Lancet* **1**, 1239
COOKE W T (1955) *Proc roy Soc Med* **48** 484
CRAFOORD C and FRENCKER P (1939) *Acta otolaryngol* **27**, 422
DALY B M (1947) *Amer J Surg* **55** 238
EISEMAN B (1954) Discussion on McDermott *et al* *Ann Surg* **140** 539
FELDBERG, W and SHERWOOD S L (1954a) *J Physiol* **123** 148
FELDBERG W and SHERWOOD S L (1954b) *J Physiol* **125** 488
FOULK W T BUTT H R., STAUFFER M H BAGGENSTOSS A H and GROSS, J B (1955) *Gastroenterology* **29** 171
FUCHS, A (1921) *Wien med Wchnschr* **71** 710
FULD H (1933) *Klin Wchnschr* **12** 1364
GABUZDA, G J, PHILLIPS G B and DAVIDSON C S (1952) *New England J Med* **246**, 124
GOULD J (1954) *Proc roy Soc Med* **47** 215
GOULD J (1955) *Proc roy Soc Med* **48** 487
HAHN M MASSEN O NENCKI M and PAVLOV J (1893) *Arch exper Path u Pharmacol* **32** 161
JONES C M (1936) *Am J digest Dis* **3** 604
KIRK E (1936) *Acta med scandinav* Suppl 77 p 74
KREBS H A (1935) *Biochem J* **29** 1951
MACBETH R G (1955) *Brit med J* **ii** 877
MAGNUS ALSLEBEN E (1920) *Ergebn d Physiol* **18** 52
McDERMOTT W V Jr ADAMS R D and RIDDELL A G (1954) *Ann Surg* **140** 539
McDERMOTT W V Jr ADAMS R D and RIDDELL A G (1955) *Proc Soc exp biol med* 88 380
NEEFE J R. (1950) *Macy Foundation Rep* p 61
PHEMISTER D B and HUMPHREYS E M (1947) *Ann Surg* **126** 397
PHILLIPS G B SCHWARZ R GABUZDA G R and DAVIDSON C S (1952) *New England J Med* **247** 239
POLAK A In the press
RAPPAPORT A M (1951) *Macy Foundation Rep* p 161
RAPPAPORT A M BOROWY Z J and LOTTO W N (1952) *S Forum* p 504
RIDDELL A G KOPPLE P N and McDERMOTT W V Jr (1954) *Surgery* 36 675

with the mucosal valve as the best candidate, but it still lacks visual confirmation

Activity of the Lower Oesophagus

Before discussing further the nature of the barrier that prevents the oesophageal transmission of gastric pressure, or the reflux of gastric contents, I shall give an account of the activity of the oesophagus with particular reference to its lower end

The region is rather inaccessible, and for the most part we must infer its behaviour from observation of swallowed radio opaque substances, and from records of pressure changes within the lumen Such records are easily made through small water filled polythene tubes attached to suitable manometers (Plate XXVII, Figure 1) [1]

When a subject is not eating or drinking swallowing move ments occur every few minutes but for most of the time the pharynx and oesophagus are quiescent The oesophagus is then empty and collapsed being sealed off from the atmospheric pressure by the cricopharyngeal sphincter and from the intra gastric pressure by the cardiac barrier, whose nature need not at once concern us The intra oesophageal pressure is therefore virtually the same as the intrapleural pressure, and undergoes similar fluctuation during respiration Since during inspiration the intra abdominal pressure rises while the intrathoracic falls, the respiratory fluctuations are useful in showing on which side of the pressure barrier a recording site lies and whether the barrier is working properly It is obviously necessary to allow for the respiratory effects before attributing pressure changes to oesophageal activity, and to this end it is usually desirable to record respiratory movements simultaneously

Let us suppose a subject drinks some barium cream while we observe its passage radioscopically and record the pressure changes at various sites (Figure 2) The subject drinks in a series of gulps, and with each we can record the relaxation of the cricopharyngeal sphincter and observe the entry of fluid into the oesophagus Below the pharynx the intra oesophageal pressure everywhere rises sharply to atmospheric and oscillates irregularly

[1] The plates referred to in this lecture will be found between pp 400–1

XXII

The Physiology of the Lower Oesophagus and Cardia

A C DORNHORST

THE main fact about the lower oesophagus and its junction with the stomach is this as one drinks, fluid falls unhindered into the stomach but if one then stands on *one's head it remains trapped and does not re enter the oesophagus* There is obviously some special mechanism at the oesophageal gastric junction

The surprisingly diverse views of the nature of this mechanism involve one of the following assumptions (1) an extrinsic *sphincter formed by the muscle of the diaphragmatic hiatus,* (2) an intrinsic sphincter formed by specialization of the lower oesophageal muscle, (3) a valve formed by the angle between oesophagus and stomach, maintained by support from the liver or by contraction of the well developed sling muscle which runs along the lesser curve and loops round the oesophageal gastric junction, (4) a valve formed of mucosa and submucosa only, and maintained by the muscularis mucosae

In my opinion the evidence is against occlusion of the oesophagus by the diaphragmatic hiatus in normal circumstances There certainly is specialization *of the lowest part of the oesophageal* muscle, which I shall describe in detail later but the prevention of gastric reflux is apparently independent of this The whole concept of a valve formed by an acute angle of oesophageal entry is a mistake arising from thinking of a three dimensional *problem in two dimensions only* We are thus left

PLATE XXVII

(a)



(b)

FIG 1 Tubes used for simultaneous recording of intra oesophageal pressure at several sites Each tube is 1 mm in external diameter The closer view (b) shows the lateral hole forming the lowest of the recording sites The distal ends of the tubes are filled with mercury

as the fluid passes down At the last gulp of the series the crico pharyngeal sphincter contracts with more than normal vigour for a few seconds, and this contraction spreads to the top of the oesophagus to initiate a propulsive wave

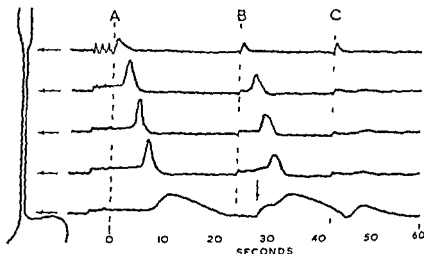


FIG 2 Composite diagram of pressure changes as recorded at different levels in the oesophagus Respiratory fluctuations have been omitted A Propulsive wave initiated by the last of a series of gulps B Propulsive wave combined with synchronous contraction of lower oesophagus (marked by arrow) C. Failure of propulsive wave synchronous contraction preceded by relaxation

The point to note here is that the propulsive wave is not initiated until the end of a series of gulps—say six, lasting about ten seconds and involving perhaps 300 ml of fluid Most of the fluid passes by gravity straight into the stomach with no delay, and the propulsive wave has little to do (Plate XXVIII, Figure 3) Of course this is not so when a solid bolus is swallowed

We may now trace the propulsive wave down the oesophagus It travels at a steady rate of about 4 cm /sec restoring as it passes, the original negative pressure (Plate XXIX Figure 4) There is little change in shape or amplitude until the last 2–3 cm are reached here the pressure developed is usually less but lasts much longer, taking perhaps 30 sec to disappear, and in fact the resting state is not regained for about one minute (Plate XXX, Figure 5) That this is so is seen when a further

PLATE XXIX

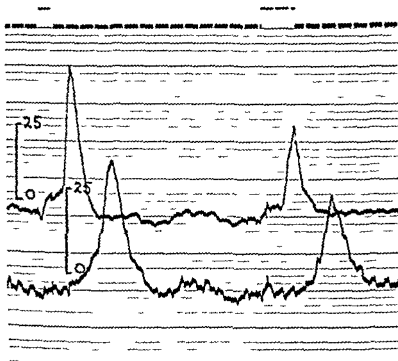


Fig 4 Propulsive waves passing down central oesophagus The recording sites are 10 cm apart In this and subsequent records time is marked in seconds and the pressure scale is in mm Hg



FIG 3 Swallowing through a relaxed oesophagus The mercury filled ends of recording tubes can be seen Only 0 5 second separates the two pictures there is no hold up of barium Compare Fig 7 (Reproduced by courtesy of *The Lancet*)

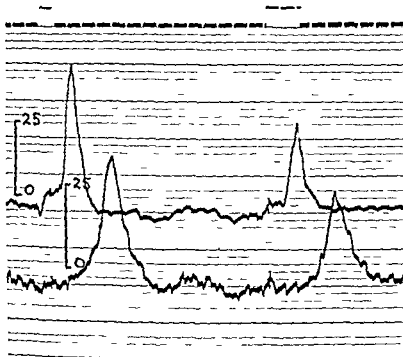


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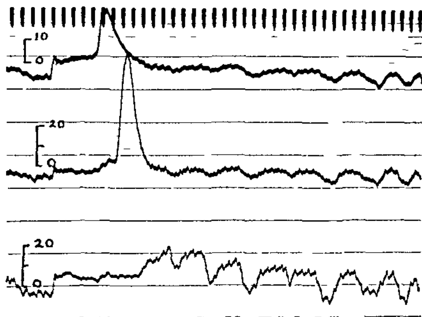


FIG 5 Pressure approximately 16 and 24 cm below pharynx and at extreme lower end of oesophagus The prolonged low pressure rise and the exaggerated respiratory variation are typical of the latter region The rise in pressure here at the movement of swallowing indicates the region was initially relaxed

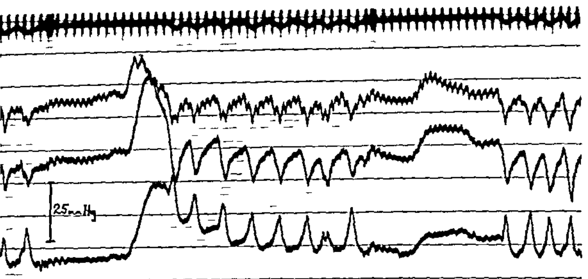


FIG. 6 The *upper* trace overlying the time marker records respiration (*inspiration downwards*). The next *two* traces record pressure at sites 9 mm apart in the lowest part of the oesophagus. The lowest trace is from a site a further 6 mm down and on the gastric side of the pressure barrier as shown by the inspiratory rises of pressure. The breath has been held for several seconds after each swallow. The first swallow *leads to a* propulsive wave arriving at the *cardiac region* in 8–9 seconds. The second swallow provokes only a *synchronous contraction* at 4 seconds preceded by probable relaxation

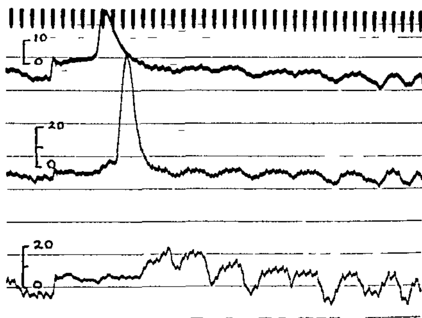


FIG 5 Pressure approximately 16 and 24 cm below pharynx and at extreme lower end of oesophagus The prolonged low pressure rise and the exaggerated respiratory variation are typical of the latter region The rise in pressure here at the movement of swallowing indicates the region was initially relaxed

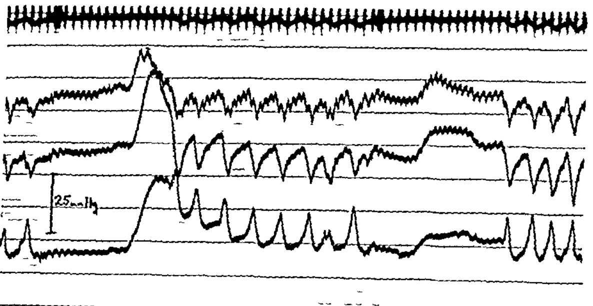


Fig 6 The upper trace (overlying the time marker) records respiration (inspiration downwards) The next two traces record pressure at sites 9 mm apart in the lowest part of the *oesophagus* The *lowest trace is from a* site a further 6 mm down and on the gastric side of the pressure barrier as shown by the inspiratory rises of pressure The breath has been held for several seconds after each swallow The first swallow leads to a propulsive wave arriving at the cardiac region in 8–9 seconds The second swallow provokes only a synchronous contraction at 4 seconds preceded by probable relaxation



Fig 7 Swallowing about 7 seconds after a propulsive wave has reached the lower end of the oesophagus there is a definite hold up of barium which lasted about 2 seconds Compare Fig 3

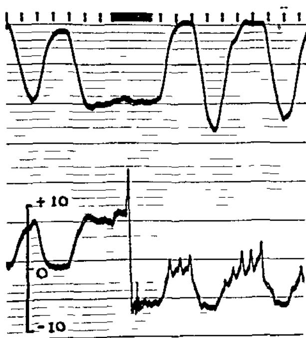


Fig 8 Upper trace respiration with inspiration downwards Lower trace pressure recorded through an open ended tube The end of the tube is at first on the gastric side of the pressure barrier At the signal the tube is withdrawn about 1 cm and enters the oesophagus

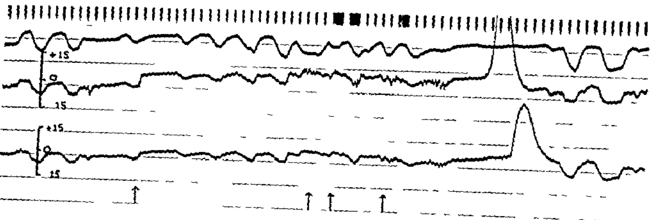


FIG 9 Upper trace respiration Pressures recorded from middle and lower oesophagus About a minute earlier air had been injected into the stomach The first arrow indicates the opening of the cardiac valve with consequent abrupt rise of pressure as the oesophagus fills with air The falls in pressure with the next few inspirations show that the valve closes again but it opens as indicated by further arrows and the signals indicate eructation of gas A propulsive wave by forcing gas back into the stomach finally restores the original low pressure

PLATE XXXIV



FIG 10 Section through cardia oesophagus above (Reproduced by courtesy of *The Lancet*)

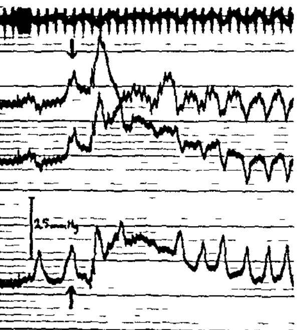


FIG 11 As for Fig 6 Note at arrow the inversion of the respiratory pressure change on the oesophageal side of the barrier

swallow is made within this period The propulsive wave though probably somewhat smaller proceeds as before but in the lower few cm differences are found First, there is no immediate rise of pressure at the moment of swallowing then about four seconds later, that is four to five seconds before the arrival of the propulsive wave, there is a synchronous rise in pressure over the lower 5 cm or so, which continues up to and merges into the propulsive wave This rise may be preceded by a short drop in pressure If a swallow follows another at a still shorter interval there may be no propulsive wave, but the synchronous contraction of the lower end may still occur (Plate XXXI, Figure 6) When fluid is drunk before the resting state is regained, a column of several cm is definitely held up for a second or two before it can enter the stomach (Plate XXXII, Figure 7)

The conclusion is therefore that when a minute or more has elapsed since the last propulsive wave, the lower oesophagus is inert, but at shorter intervals some contraction lingers even after the local pressure rise has ceased Moreover in this state swallowing induces further synchronous contraction independent of the propulsive wave and at least sometimes preceded by relaxation This effect might be nervously mediated, or might be caused by the stretch associated with the pharyngeal elevation of swallowing

The dependence of oesophageal behaviour on frequency of swallowing is responsible I think, for some apparent discrepancies in the accounts of different authors and one may add that repeated swallowing of sips of water eventually lead to small and irregular responses A few minutes rest or the swallowing of something solid restores the original pattern

The Pressure Barrier

I now turn to the behaviour and nature of the cardiac pressure barrier

The following experiment, which has been performed several times by my surgical colleague Mr Kent Harrison, shows that whatever may be the effect of structures extrinsic to the stomach and oesophagus, there is certainly an effective intrinsic mechanism During laparotomy the stomach is filled with water through

an oesophageal tube which is then withdrawn With the pylorus clamped, the distended stomach may now be firmly squeezed between the hands without emptying into the oesophagus Moreover this remains true even when the cardia and lower oesophagus have been completely mobilized as required in some operations, in which case there is no support from neighbouring structures, and the oesophagus makes approximately a right angle with the gastric fundus It is clear that extrinsic factors are not necessary for cardiac competence This is not to assert that the maintenance of normal anatomical relations is not helpful, and there is in fact no doubt that when they are disturbed for example in hiatus hernia, cardiac incompetence is frequent though not invariable

Pressure measurements show that the barrier separating gastric and oesophageal pressures is remarkably narrow a pair of recording sites 5 mm apart span it comfortably Tubes may be slid through it easily in the forward direction even during inspiration where a considerable pressure step is present On withdrawal from the stomach one often records a small spike of pressure followed by a very sharp drop (Plate XXXII, Figure 8) In the immediate vicinity of the pressure barrier and on either side of it the respiratory pressure swings are exaggerated, presumably because the recording site moves in and out of the actual barrier region An unexpected finding is that the contraction of the lower oesophageal muscle may be recorded on the gastric side of the barrier for a distance of about 1 cm (Plate XXXI, Figure 6)

The valvular nature of the barrier is striking It is impossible to maintain a pressure in the oesophagus above that in the stomach, but gastric contents cannot be forced back by the considerable inverse pressures that may be applied By contrast the valve may open spontaneously from time to time This may be provoked by injecting air into the stomach by fizzy drinks or by the classical carminatives such as dill water The opening of the valve is signalled on the record by a sudden rise of oesophageal pressure to approximately the gastric level and the appearance of inspiratory rises of pressure—that is the pressure within the oesophagus now follows that in the stomach (Plate

XXXIII, Figure 9) Such cardiac opening occurs quite suddenly for a few breaths and then intermits Since the entry of gastric contents into the oesophagus commonly provokes a propulsive wave which traps it and forces it back cardiac opening often does not lead to eructation

The Valve

At this stage I had better say what sort of structure I think the valve has Plate XXXIV Figure 10, an operative specimen may be a lucky fluke but it illustrates what I have in mind A funnel of mucosa pulled up and maintained by specialized action of the muscularis mucosae would have the properties described It can be seen that a very modest pressure exerted by the muscularis mucosae would maintain valvular action Moreover a recording site in the lower part of the funnel would reflect gastric pressure variations while still subject to direct squeezing by oesophageal muscle Such a valve could be opened by inhibiting the con traction of the muscularis mucosae by relaxation of the main stomach muscle pulling out the folded mucosa from below, and perhaps by contraction of the muscularis mucosae of the oeso phagus pulling it out from above

Does the proper functioning of the cardiac valve depend on the specialized behaviour of the lower oesophageal muscle? Apparently not for not only does the valve remain competent when all muscular activity following swallowing has subsided but patients with symmetrical progressive scleroderma, in whom the lower oesophageal muscle characteristically atrophies with complete lower oesophageal paralysis often have normally com petent cardias Moreover during the synchronous lower oeso phageal contraction described earlier the cardia may actually open for a second or two (Plate XXXIV Figure 11) This may perhaps be evidence of activity in the lower oesophageal muscularia mucosae

There is still much to be learnt about this region and rapid progress may be expected by simultaneous use of multiple pressure recording and cineradiography which the introduction of the image intensifier has now made feasible

XXIII

Renal Control of Acid-base Balance

M D MILNE

THE maintenance of an almost constant hydrogen ion concentration in the blood and extracellular fluid is one of the most important physiological homeostatic mechanisms In health, the pH of the plasma varies from 7 35 to 7 45 Death in acidotic coma usually occurs if the pH falls below 7 0, and, at the other extreme, a value of 8 0 is equally lethal Information regarding intracellular pH is less accurate, but there is no doubt that the body cells are more acid than the plasma Quantitatively, voluntary muscle is the most important type of cell, since it accounts for 35 per cent of the total body solid Gardner, MacLachlan and Berman (1952) found the average pH within the muscle fibre was 6 98, which means that the concentration of intracellular hydrogen ion is about 2 5 times that of the plasma The concentration gradient of hydrogen ion across the cell membrane is increased in states of potassium deficiency, since loss of potassium is corrected by transfer of both sodium and hydrogen ion into the cell (Cooke, Segar, Cheek, Coville and Darrow, 1952) Values as low as pH 6 4 have been recorded in voluntary muscle from potassium depleted animals (Gardner *et al*, 1952)

Any abrupt change in body pH is prevented by extracellular buffer systems, especially bicarbonate and plasma proteins, and by intracellular buffers including tissue proteins, phosphatic esters, and the haemoglobin of the erythrocytes The actual pH of any buffer system is determined by the Henderson Hasselbalch equation

$$\mathrm{pH} - \mathrm{pK} = \log \frac{[\text{ionized salt}]}{[\text{free acid}]},$$

where pK_a is a constant numerically equal to the pH at which there is equal concentration of ionized salt and free acid Graphs of this equation relating to buffer systems of especial importance in renal physiology are shown in Figure 1 The equation relating

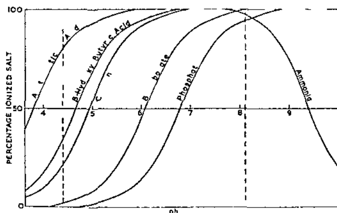


FIG 1 Graph of equation $\mathrm{pH} - \mathrm{pK_a} = \log \frac{[\text{ionized salt}]}{[\text{free acid}]}$ for various buffer systems of importance in renal physiology Since ammonia is a weak base the equation in this case is $\mathrm{pK_a} - \mathrm{pH} = \log \frac{[\text{ammonium salt}]}{[\text{free ammonia}]}$ The vertical broken lines are the extreme upper and lower ranges of urinary pH

to plasma bicarbonate and carbonic acid is of great physiological importance The concentration of carbonic acid in arterial blood is proportional to the partial pressure of carbon dioxide, which is kept constant at 40 mm of mercury by control of the depth and rate of pulmonary ventilation Similarly, the plasma bicarbonate is maintained at a level of from 26 to 28 mEq /l by the renal mechanisms reviewed in this lecture Any alterations in the partial pressure of carbon dioxide imposed by lung disease voluntary hyperventilation or breathing excess carbon dioxide causes a corresponding change in plasma bicarbonate Similarly a primary alteration of plasma bicarbonate from renal disease, metabolic abnormalities or ingestion of acid or alkali will result in a compensatory change of partial pressure of carbon dioxide by appropriate adjustment of ventilation This tendency to proportionate variation between plasma

bicarbonate and carbon dioxide reduces, but does not completely prevent, potentially harmful pH changes of blood and extracellular fluid

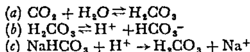
Whilst the chemical buffer systems are invaluable in reducing the rate and extent of reaction changes within the body, they cannot prevent the effects of cumulative additions of acid or alkali In the general processes of metabolism about 20 mols of acid in the form of carbon dioxide is formed each day by oxidation of carbohydrates, fats and proteins This is eliminated by the lungs in the expired air In addition, from 50 to 100 mEq of non volatile acid is produced daily as phosphate from phospholipid metabolism, and as sulphate from oxidation of sulphur containing amino-acids In starvation, and to a much greater degree in diabetic ketosis, considerable quantities of acetoacetic and β hydroxybutyric acids are formed from incomplete oxidation of fats These acidic metabolic products are excreted in the urine

In this lecture inorganic electrolytes except ammonium and bicarbonate, e g sodium, potassium, calcium, magnesium, chloride, sulphate and phosphate, will be referred to as 'fixed *anions or cations Ammonium, bicarbonate and organic acids* will be termed 'labile electrolytes since these substances can be produced or destroyed by metabolic processes Metabolic acidosis is a state in which there has been accumulation of fixed anion in excess of cation, and metabolic alkalosis is the reverse condition The pH of plasma and extracellular fluid is usually decreased in acidosis and increased in alkalosis In potassium depletion however, despite a total body acidosis from loss of base, the plasma bicarbonate and pH are often increased owing to transfer of hydrogen ion into cells The misleading term of 'hypokalaemic alkalosis is often applied to this condition

Bicarbonate Excretion and Reabsorption

Since the glomerular filtration rate in the normal adult is about 120 ml per minute and the plasma bicarbonate is 26 to 28 mEq /l, about 3 3 mEq of bicarbonate ion is filtered through the glomeruli *each minute Usually the urine is acid and contains* virtually no bicarbonate, all the filtered bicarbonate having

been reabsorbed by the renal tubular cells Bicarbonate re absorption is now considered to be carried out by a process of exchange of hydrogen ion produced from carbonic acid within the tubular cells, for sodium ion within the tubular lumen The reactions involved are



(a) $CO_2 + H_2O \rightleftharpoons H_2CO_3$

(b) $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

(c) $NaHCO_3 + H^+ \rightarrow H_2CO_3 + Na^+$

The hydration of carbon dioxide to carbonic acid is a relatively slow process but is greatly accelerated within the cell by the enzyme, carbonic anhydrase This enzymatic reaction can be partially inhibited by the drug acetazolamide In therapeutic doses of from 3 to 15 mg /Kg body weight, only about 20 per cent of the filtered bicarbonate appears in the urine (Counihan, Evans and Milne 1954), but this fraction can be raised to 50 per cent or more by use of larger doses in dogs This suggests that tubular reabsorption of bicarbonate is chiefly if not en tirely, dependent on exchange of hydrogen ion for sodium ion

The final urinary reaction therefore depends on the balance between the amount of bicarbonate filtered at the glomeruli and the hydrogen ion secreted by the tubule cells An increase of plasma bicarbonate will tend to produce an alkaline urine, whilst increase of secreted hydrogen ion will cause greater bicarbonate reabsorption and an acid urine When the two factors are antagonistic the influence of hydrogen ion secretion is usually predominant

Typical examples of stimuli causing variation in urinary pH are shown in Table 1 Metabolic acidosis is caused by the direct addition of acidic radicles as in diabetic ketosis or after ingestion of ammonium chloride Plasma bicarbonate is reduced and the urine becomes strongly acid Conversely in metabolic alkalosis e g after ingestion of sodium bicarbonate, plasma bicarbonate is increased and the urine becomes alkaline

In reaction changes of respiratory origin e g after hyper ventilation or breathing 5 per cent carbon dioxide there is a profound alteration in the partial pressure of carbon dioxide in

both alveolar air and arterial blood This changes the concentration of substrate for production of hydrogen ion by carbonic anhydrase It has been shown (Brazeau and Gilman, 1953, Relman, Etsten and Schwartz, 1953, Dorman, Sullivan and Pitts, 1954) that bicarbonate reabsorption, and therefore tubular secretion of hydrogen ion, is directly proportional to the

TABLE 1 Effect of various stimuli on the reaction of the urine

	Plasma bicarbonate	Hydrogen ion exchange	Urinary reaction
Sodium bicarbonate	Raised	Normal	Alkaline
Ammonium chloride	Reduced	Normal	Acid
Hyperventilation	Reduced	Reduced	Alkaline
Respiratory acidosis	Raised	Raised	Acid
Potassium chloride	Reduced	Reduced	Alkaline
Potassium depletion	Raised	Raised	Acid
Acetazolamide	Reduced	Reduced	Alkaline
Sodium sulphate (normal subject)	Normal	Slightly raised	Slightly acid
Sodium sulphate (sodium depletion)	Normal	Considerably raised	Strongly acid

partial pressure of carbon dioxide in arterial blood Therefore, after hyperventilation the urine is alkaline despite a reduction of plasma bicarbonate Conversely, after inhalation of 5 per cent carbon dioxide or in chronic respiratory failure from emphysema, the urine is acid although the plasma bicarbonate is increased

Potassium depletion or excess has a profound influence on acid base balance and particularly causes change of intracellular reaction After ingestion of potassium chloride, potassium ion passes into the cells whereas chloride remains in the extracellular compartment This causes an increase of intracellular pH with an extracellular acidosis Owing to reduction

of hydrogen ion available for exchange, the urine becomes alkaline despite a fall of plasma bicarbonate Diminished hydrogen ion secretion may be interpreted either as directly due to increased alkalinity of renal cells or as secondary to increased exchange of potassium ion Berliner, Kennedy and Orloff (1951), who favour the latter alternative consider that potassium and hydrogen ion share a common exchange mechanism and that increased exchange of one ion will inevitably depress that of the other In potassium depletion, the renal tubule cells are more acid from loss of intracellular cation (Anderson and Mudge 1955) There is enhanced exchange of hydrogen ion and the urine is acid despite an extracellular alkalosis with increase of plasma bicarbonate (Roberts, Randall, Sanders and Hood 1955)

Rapid acidification of the urine may be produced by infusions of sodium salts of variously rapidly excreted anions e g sodium sulphate sodium phosphate, and sodium p amino-hippurate The effect is much more evident in subjects depleted of sodium or in patients with oedema and sodium retention (Schwartz Jenson and Relman, 1955) Both hydrogen ion and potassium ion are exchanged in excess for sodium ion within the tubular lumen

Quantitative Aspects of Hydrogen Ion Excretion

Excretion of hydrogen ion is numerically equal to the sum of urinary titratable acidity and ammonia excretion less urinary bicarbonate This amount is equivalent to the excess of fixed anion over fixed cation Since neither urinary titratable acidity nor ammonia can be excreted in unlimited quantities elimination of excess hydrogen ion cannot exceed a certain maximal value If the rate of accumulation of acid is greater than this e g in severe diabetic ketosis progressive acidosis and death is liable to occur

Titratable acidity rises with increased excretion of urinary buffers and with reduction of urinary pH The minimum urinary pH is about 4 4, corresponding to a concentration gradient of hydrogen ion from urine to plasma of one thousand to one As will be shown later urinary acidification is impaired in

potassium deficiency, the urinary pH being limited to values above 5 2 or 5 4

In urine of pH between 5 8 and 7 4, phosphate accounts for almost all of the titratable acidity, but in more acid urine, organic acids, e g creatinine, uric acid and citric acid, become

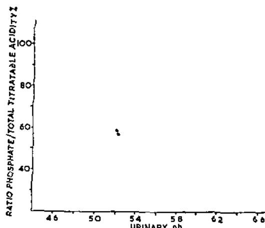
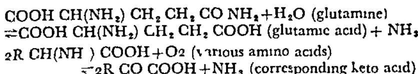


FIG 2 Percentage of titratable acidity due to phosphate at varying urinary pH At pH values of above 5 8 phosphate accounts for almost the whole of urinary titratable acidity At lower pH values organic acids become progressively more important and phosphate accounts for a much smaller fraction

equally important (Figure 2) Except in conditions where urinary buffer is artificially increased, e g the infusion of phosphate in acidotic subjects (Pitts, Lotspeich, Schiess and Ayer, 1948), titratable acidity is of less importance than urinary ammonia in the excretion of hydrogen ion and is almost always *less than 100 mEq per day*

AMMONIA SYNTHESIS AND EXCRETION

There is little if any free ammonia in arterial blood (Conway, 1950), urinary ammonia being formed within the distal tubule cells by the following reactions



$COOH\ CH(NH_2)\ CH_2\ CH_2\ CO\ NH_2 + H_2O$ (glutamine)
$\rightleftharpoons COOH\ CH(NH_2)\ CH_2\ CH_2\ COOH$ (glutamic acid) $+ NH_3$

$2R\ CH(NH\ )\ COOH + O_2$ (various amino acids)
$\rightleftharpoons 2R\ CO\ COOH + NH_3$ (corresponding keto acid)

The former reaction is catalysed by the enzyme glutaminase, and the latter by amino-acid oxidase In the dog, the hydrolysis of glutamine to glutamic acid accounts for about 60 per cent of urinary ammonia (van Slyke, Phillips, Hamilton Archibald Futcher and Hiller 1943), but it is not certain whether this applies in man

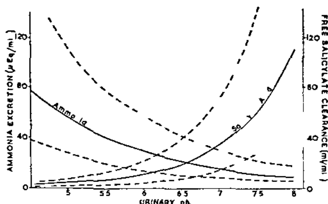


FIG 3 Variation in ammonia excretion and in free salicylate clearance with respect to urinary pH Continuous line is the calculated logarithmic regression line in adult subjects broken lines give the limits at twice the standard deviation Excretion of ammonia increases in acid urine excretion of *salicylic acid increases in alkaline urine Data for ammonia from* Clarke *et al* (1955) data for salicylic acid from Macpherson *et al* (1955)

Ammonia is one example of a group of weak bases or acids in which excretion is greatly influenced by urinary pH The bases include ammonia, quinine nicotine, mepacrine and procaine and the acids, salicylic acid and gentisic acids The excretion of the weak bases is increased in acid urine, the logarithm of excretion being inversely proportional to the urinary pH (Clarke Evans, MacIntyre and Milne 1955) Conversely, excretion of the weak acids is greater in alkaline urine (Macpherson Milne and Evans, 1955) Average adult excretion rates in the cases of ammonia and salicylic acid are given in Figure 3 The excretory mechanism involved is a process of *diffusion* across the cell membrane into the urine within the distal tubular lumen The membrane is freely permeable to the unionized fraction but is impermeable to the ionized component

(Macpherson *et al*, 1955) In the case of ammonia, free ammonia is synthesized within the tubule cells and diffuses inwards to the urine and outwards to the peri tubular fluid and renal capillary blood In highly acid urine, owing to increased ionization at low pH, more ammonia must diffuse before equilibrium of the unionized component is reached, and there fore excretion automatically increases

TABLE 2 Factors affecting the rate of ammonia excretion and the concentration of ammonia in the renal venous blood

(a) Factors affecting ammonia transport	Urinary ammonia	Blood ammonia
Increased urinary acidity	Increased	Decreased
Increased urinary alkalinity	Decreased	Increased
Oliguria	Decreased	Increased
Polyuria	Increased	Decreased
(b) Factors affecting ammonia production	Urinary ammonia	Blood ammonia
Systemic acidosis	Increased	Increased
Systemic alkalosis	Decreased	Decreased
Potassium depletion	Increased	Increased
Acetazolamide	Increased	Increased

In metabolic acidosis, ammonia excretion rapidly rises as the urine becomes highly acid With continued acidosis however, excretion rises still further despite a constant low urinary pH This is due to a gradual increase of glutaminase and amino acid oxidase content of renal tubule cells with consequent rise of ammonia production (Davies and Yudkin, 1952) A similar increase has been shown to occur in potassium depletion (Iacobellis, Muntwyler and Griffin 1954) and after prolonged ingestion of acetazolamide (Rector Seldin Roberts and Copen haver, 1954) The common stimulus is an increased acidity of the renal tubule cells Factors influencing ammonia excretion can therefore be divided into those modifying transport into the

urine and those modifying rate of production within the cell (Table 2) Greater production by rise of renal glutaminase and amino acid oxidase will increase diffusion both to the urine and the renal capillary blood Increased transport into highly acid urine will diminish diffusion outwards to the blood In contrast to the great physiological importance of urinary ammonia, passage of ammonia into the renal venous blood is usually of no significance since it is rapidly converted to urea by circulation through the liver It can however occasionally be of importance in hepatic failure, when an increase of blood ammonia may precipitate hepatic coma The concentration of ammonia in the renal venous blood will be greatest when production is at a maximum but transport to urine is minimal This combination occurs during continued ingestion of acetazolamide which causes a systemic acidosis with an alkaline or neutral urine Many substances containing large amounts of nitrogen are known to precipitate hepatic coma, e g proteins, amino acids ammonium chloride and urea Acetazolamide is the only known substance which will cause hepatic coma despite an almost negligible nitrogen content (Webster 1955)

Although urinary ammonia can increase much more than can urinary titratable acidity it cannot rise above a certain limiting value imposed by the rate of supply of substrate If it is assumed that 60 per cent of urinary ammonia is produced from glutamine it can be calculated that the greatest possible rate of ammonia synthesis would be approximately 650 μEq per minute This assumes that all plasma glutamine is converted to ammonia in one circulation through the kidney which in fact never occurs Even in severe prolonged acidosis the maximum rate of ammonia excretion is rarely greater than 250 μEq per minute corresponding to an output of about 350 mEq per day Since titratable acidity is almost invariably less than 100 mEq per day it follows that the maximum limit of elimination of hydrogen ion by the kidneys is about 450 mEq daily This corresponds to a daily intake of 24 g of ammonium chloride A greater intake would inevitably lead to a progressive and eventually fatal acidosis In renal failure both the capacity to secrete an acid urine and to synthesize ammonia are greatly

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of the kidney to produce a high concentration gradient of hydrogen ion between urine and plasma In Figure 5 urinary pH during the first three days of ammonium chloride ingestion in a normal subject is compared with that obtained in similar

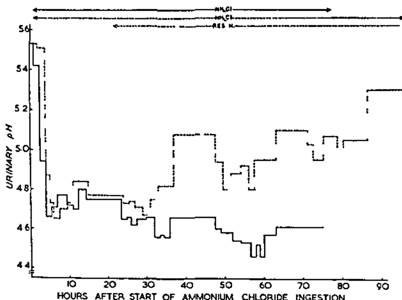


FIG 5 Comparison of urinary pH values during ammonium chloride acidosis in the same subject on a normal diet (continuous line) and on a low potassium diet (broken line) As the potassium depletion becomes pro gressively more severe the urinary pH becomes steadily higher and diver gent from that of the normal control Reproduced from paper by Clarke *et al* (1955) by permission of the editor of *Clinical Science*

circumstances during potassium depletion Urinary pH falls to values below 4 5 in the normal subject, but becomes fixed at between 5 2 and 5 4 in potassium depletion Total excretion of hydrogen ion is however unimpaired since owing to increased cellular acidity ammonia excretion remains adequate despite an abnormally high urinary pH Other renal functional defects which have been recorded in potassium depletion (Schwartz and Relman 1953) include failure of osmotic concentrating power and reduction of glomerular filtration rate renal blood flow and Tm_{PAH} (tubular maximal reabsorptive capacity for

impaired Severe acidosis can therefore be caused by therapeutic doses of ammonium chloride which are quite harmless in the normal subject In terminal renal failure, the damaged kidneys become unable to compensate for the relatively small amount of fixed acid produced in normal metabolism, and death in uraemic coma then occurs The limited ability of the kidneys to excrete acid will later be compared with an apparently *almost unlimited capacity to excrete alkali*

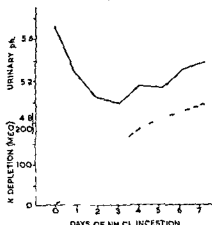


FIG 4 Effect of continuous ingestion of 8 g ammonium chloride daily on urinary pH and on cumulative potassium balance Urinary pH reaches a minimum value on the second or third day of acidosis and increases thereafter Data calculated from results of Wood (1955)

HYDROGEN ION EXCRETION IN STATES OF POTASSIUM DEPLETION

If ammonium chloride is taken at a constant moderate dosage, e g 8 g daily, the urinary pH falls and usually reaches a *minimum* value below pH 4 8 *on the second or third day* of acidosis (Figure 4) Thereafter, the urinary pH steadily rises until it stabilizes at a pH of between 5 2 and 5 4 despite continued ammonium chloride ingestion and acidosis (Wood 1955) There is always a negative balance of both sodium and potassium during the first few days of ammonium *chloride* ingestion and it was thought possible that the acidification defect could be due to electrolyte depletion Clarke *et al* (1955) showed that sodium depletion had no such effect but in potas*sium depletion there was progressive* impairment in the ability

in mEq per ml and V is the urinary volume in ml per minute

Since the glomerular filtration rate remains almost constant, the plasma bicarbonate varies directly with the amount of bicarbonate excreted When equilibrium is reached, the amount of bicarbonate excreted equals the amount ingested Thus the plasma bicarbonate concentration produced by a given rate of bicarbonate ingestion can be predicted Figure 6 shows the relationship between these two variables for glomerular filtration rates of 30, 60 and 120 ml per minute It is seen that in normal subjects, very large doses of sodium bicarbonate of over 1,000 mEq per day are necessary to raise the plasma bicarbonate to values of above 35 mEq /l Sodium bicarbonate intake of this order, corresponding to about 100 g per day, is not tolerated by mouth but can be given dissolved in a milk intragastric drip in the treatment of duodenal ulcer (van Goidsenhoven Gray Price and Sanderson 1954) This amount is necessary if it is desired to neutralize gastric hydrochloric acid completely The increase of plasma bicarbonate agrees well with that expected by theory (Figure 6) In fact the increase is usually a little less than the expected amount owing to increase of glomerular filtration rate during high sodium intake These observations show that the normal subject can excrete large amounts of alkali without severe symptoms or any profound disturbance of biochemical homeostasis The capacity to excrete acid is much more limited, and therefore severe acidosis is more common in clinical medicine than is uncontrolled alkalosis

In renal failure, with reduction of the glomerular filtration rate the capacity to excrete alkali becomes progressively impaired and plasma bicarbonate rises much more rapidly after alkali ingestion (Figure 6) In potassium deficiency owing to increased cellular acidity with enhanced exchange of hydrogen ion bicarbonate reabsorption is excessive and therefore the capacity to excrete bicarbonate is impaired Comparatively small doses of sodium bicarbonate e g 200 mEq per day will result in much larger increases of plasma bicarbonate to approximately 40 mEq /l (Evans MacIntyre Macpherson and Milne,

PAH) An adequate concentration of potassium is known to be necessary for the efficient action of adenosine triphosphate, the main source of intracellular energy In potassium depletion the function of the renal tubule cells in maintaining concentration gradients between urine and plasma appears to be particularly impaired This acidification defect is of greatest practical im portance in diabetic ketosis where there is almost invariably an associated potassium depletion Urine pH is usually fixed at pH 5 4 or above despite severe acidosis and extreme reduction of plasma bicarbonate An abnormally high urinary pH in diabetic ketosis is probably an important but hitherto neglected sign of existing potassium depletion Owing to the abnormally high pH, the keto acids can contribute very little to urinary titratable acidity with consequent impairment of hydrogen ion excretion and intensification of the existent acidosis (Clarke *et al*, 1955)

Quantitative Aspects of Alkali Excretion

Whilst acid can only be excreted by active secretion of hydrogen ion (Pitts *et al*, 1948), alkali is excreted by an increase of bicarbonate in the glomerular filtrate Alkali is therefore excreted with less difficulty than acid, and there is no definite upper limit of excretory capacity as in the elimination of acid After ingestion of sodium bicarbonate the plasma bicarbonate and consequently the amount filtered are increased, but hydro gen ion secretion remains unchanged Normally, the whole of the filtered bicarbonate is reabsorbed by hydrogen ion exchange Therefore

$$G F R \times P_{HCO_3} - H^+ = O$$

where G F R is the glomerular filtration rate in ml per min ute, P_{HCO_3} is the plasma bicarbonate in mEq per ml, and H^+ is the amount of hydrogen ion secreted by the tubules in mEq per minute

After bicarbonate ingestion

$$G F R \times P_{HCO_3} - H^+ = U_{HCO_3} V$$

where U_{HCO_3} is the concentration of bicarbonate in the urine

chloride acidosis, in potassium deficiency, and after acetazolamide ingestion and, conversely, is increased when the cells are alkaline Organic acid excretion does therefore rise during metabolic alkalosis from bicarbonate ingestion, but in amounts almost invariably less than 20 mEq daily (Evans *et al*, 1957) Cooke Segar, Reed, Etzwiler, Vita, Brusilow and Darrow (1954) have shown that when potassium bicarbonate is administered to potassium deficient rats, there is a large increase of urinary organic acid without any increase of urinary bicarbonate A similar effect occurs in man but on a much smaller scale (Evans *et al*, 1957) The effect seems to be due to very rapid entry of potassium into cells, presumably associated with an acute rise of intracellular pH Repletion with rubidium or caesium salts which pass into depleted cells in place of potassium is an equally effective stimulus in the rat In man this renal mechanism is quantitatively of little or no importance, bicarbonate excretion being the one effective means of elimination of excess base

In summary, the kidney has been shown to be highly efficient in the maintenance of a constant extracellular pH The capacity to excrete acid is limited, and progressive acidosis inevitably results from addition of acid at a rate greater than can be eliminated in the urine There is no definite upper limit to alkali excretion, the healthy kidney being able to excrete alkali at more than three times the rate at which it can excrete acid In renal failure and in potassium depletion there is impairment of both acid and alkali excretion with a greater tendency to potentially harmful variation in plasma bicarbonate and plasma pH

REFERENCES

ANDERSON H M and MUDGE G H (1955) *J clin Invest* 34 1691

BERLINER R W KENNEDY T J and ORLOFF J (1951) *Amer J Med* 11 274

BRAZEAU P and GILMAN A (1953) *Amer J Physiol* 175 33

CLARKE E EVANS B M MACINTYRE I and MILNE M D (1955) *Clin Sci* 14 421

1957) Total alkali excretion may however remain unimpaired, the amount of bicarbonate excreted being equal to the intake Large doses of sodium bicarbonate are clearly much more toxic both in renal insufficiency and in potassium depletion

It is theoretically possible that excess alkali could be eliminated without increase of bicarbonate excretion, the excess fixed

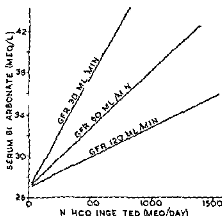


Fig 6 Graphs of equation G F R × P_{HCO_3} − H+ ≈ U_{HCO_3} V for values of glomerular filtration rate of 30 60 and 120 ml per minute From this figure the serum bicarbonate produced by any given steady rate of sodium bicarbonate ingestion can be predicted Much higher concentrations of serum bicarbonate will be found in renal failure than in the normal subject with glomerular filtration rate of about 120 ml per minute

cation being combined with organic acids This method would be comparable to the elimination of excess fixed anion as ammonium salts during acidosis It would however be a wasteful process, since organic acids are potential sources of energy This method of alkali excretion does in fact occur, but usually in negligible amounts The chief organic acids concerned, in diminishing order of importance, are citric acid, α ketoglutaric acid, and pyruvic acid (Evans *et al* 1957) Citric acid excretion in particular is greatly influenced by variation in acid base balance The reaction of the renal tubule cells rather than the pH of the urine appears to be the main determinant of the excretion rate (Clarke *et al* 1955) Citric acid excretion is diminished when renal cells are unduly acid, e g in ammonium

XXIV

Some Anomalies in Endocrine Carcinogenesis

E S HORNING

IT is actually inside a generation since the chemist and the biologist have made important discoveries on the causes of cancer, which have been responsible for directing researches into two main channels There are the extraneous agents such as the carcinogenic hydrocarbons and the ionizing radiations and the inherent agents such as the hormones, then of course there are the genetic factors which influence responsiveness to both these extrinsic and intrinsic agents

I propose to deal with the induction control and prevention of endocrine neoplasia, and I intend to discuss some of the anomalies which I have personally encountered in endocrine cancer because very often by studying the exceptions to the general rule we develop a better understanding of such elusive biological mechanisms

I should like to begin by quoting some opening remarks made by Dr Jacob Furth (1955) of the Cancer Research Foundation Boston at the recent Laurentian Conference on Hormone Research and Abnormal Growth He made the following statement Recent studies have strengthened our concept that there are two basically different types of cancer one dependent and the other autonomous

The terms hormone dependent and hormone independent cancers were first used by Huggins of Chicago to denote those neoplasms which depend upon hormones for their maintenance and those which grow independently of them Dependent

CONWAY E J (1950) *Microdiffusion Analysis and Volumetric Error* 3rd edn Crosby Lockwood London
COOKE R E, SEGAR W E, CHEEK D B COVILLE F E and DARROW D C (1952) *J clin Invest* 31, 798
COOKE, R. E, SEGAR W E REED C ETZWILER D D VITA M BRUSILOW S and DARROW D C (1954) *Amer J Med* 17 180
COUNIHAN, T B EVANS, B M and MILNE M D (1954) *Clin Sci* 13 583
DAVIES B M A and YUDKIN J (1952) *Biochem J* 52 407
DORMAN P J SULLIVAN W J and PITTS R F (1954) *J clin Invest* 33 82
EVANS B M, MACINTYRE I MACPHERSON C R, and MILNE, M D (1957) *Clin Sci* 16 53
GARDNER L I MACLACHLAN, E A and BERMAN H (1950) *J gen Physiol* 36 153
VAN GOIDSENHOVEN G M T GRAY O V PRICE, A V and SANDERSON P H (1954) *Clin Sci* 13 383
IACOBELLIS, M, MUNTWYLER E and GRIFFIN G E (1954) *Amer J Physiol* 178 477
MACPHERSON, C R. MILNE M D and EVANS, B M (1955) *Brit J Pharmacol* 10 484
PITTS, R F LOTSPEICH W D SCHIESS W A and AYER J L (1948) *J clin Invest* 27 48
RECTOR F C SELDIN D W ROBERTS A D and COPENHAVER J H (1954) *Amer J Physiol* 179 353
RELMAN A S ETSTEN B and SCHWARTZ W B (1953) *J clin Invest* 32 972
ROBERTS, K E RANDALL H T SANDERS H L and HOOD M (1955) *J clin Invest* 34 666
SCHWARTZ W B JENSON R L and RELMAN A S (1955) *J clin Invest* 34 673
SCHWARTZ W B and RELMAN A S (1953) *J clin Invest* 32 258
VAN SLYKE D D PHILLIPS R A HAMILTON P B ARCHIBALD R. M FUTCHER P H and HILLER A (1943) *J biol Chem* 150 481
WEBSTER L T (1955) *J clin Invest* 34 969
WOOD F J Y (1955) *Clin Sci* 14 81

Lacassagne in 1937, Nathanson and Andervont (1939), Cramer and Horning (1938) working independently were among the first to demonstrate that the spontaneous develop ment of mammary cancer in some strains of mice could be pre vented, and the incidence of cancer in other strains considerably reduced, by early treatment with a hormone antagonist

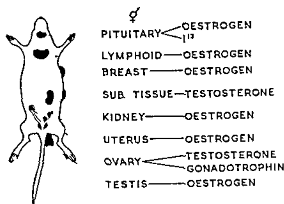


FIG 1 Endocrine carcinogenesis Diagram showing site of neoplasm together with responsible hormonal agent

In the clinical field Loeser (1940) was the first to use testo sterone in the treatment of breast cancer In 1944 Haddow and his co workers, relying on the depression of pituitary function and hence the inhibition of ovarian secretion in preference to employing a hormone antagonist, were the first to use oestrogen for the treatment of breast cancer in women This treatment was confirmed by Nathanson (1947) who found it to be effective in post menopausal women suffering from this disease Pearson (1955) in a recent review claims remis ion in 45 per cent of cases

Let us now investigate some of the experimental evidence upon which some of this work we have briefly discussed is based It is proposed to discuss the induction of tumours of the pros tate, kidney, pituitary, testes and ovary (see Figure 1) and also in some instances their prevention by using an appropriate hormone antagonist These tumours have been purposely selected because in some instances both their induction and behaviour are anomalous

neoplastic growths, as we know, arise in organs of the endocrine system or else in organs under its direct influence They are composed of cells which have been stimulated to proliferate because of a hormonal imbalance, and in many instances may be fully or partially controlled by a restoration of the normal equilibrium brought about by a readjustment of the endocrine balance

Autonomous neoplasms on the other hand, such as those which develop in the skin, stomach, lung, etc , are not under direct endocrine control nor can their growth or behaviour be influenced by any form of hormonal modification However, as in all biological problems, the dividing line between these two basically different types of cancer is not as rigid as might at first appear, because a certain number of hormone dependent tumours must obviously give rise to autonomous variants

When a tumour becomes an autonomous lesion it is composed of permanently altered cells and is freed from its sensitivity to the hormonal forces which control the cells of the endocrine dependent tumours It is of course conceivable that some malig nant growths might be composed of both the dependent and autonomous cellular components, and this might explain why a hormonal dependent tumour whose growth has previously been inhibited by means of endocrine therapy, will suddenly lose its responsiveness to a particular hormone, and become an uncontrolled autonomous neoplasm

In order to appreciate the first endocrinological approach to the cancer problem we shall have to retrace our steps back to May 1932 when Lacassagne, of the Radium Institute in Paris, published his classical discovery that the naturally occurring oestrogenic steroid hormone Oestrone was implicated in the cause of breast cancer in mice This was the first demonstration that a hormone circulating in the blood stream is capable of inducing neoplasia This experiment of Lacassagne (1932) was in fact the foundation stone in the pathway of endocrine carcinogenesis Since then, great strides have been made in the induction inhibition and prevention of certain forms of endo crine cancer in both man and animals by altering their hor monal environment

Lacassagne in 1937, Nathanson and Andervont (1939) Cramer and Horning (1938) working independently were among the first to demonstrate that the spontaneous development of mammary cancer in some strains of mice could be prevented, and the incidence of cancer in other strains considerably reduced, by early treatment with a hormone antagonist

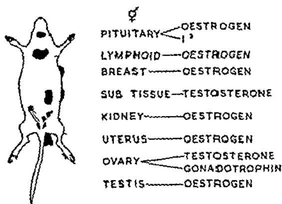


Fig 1 Endocrine carcinogenesis Diagram showing site of neoplasm together with responsible hormonal agent

In the clinical field Loeser (1940) was the first to use testosterone in the treatment of breast cancer In 1944 Haddow and his co workers relying on the depression of pituitary function and hence the inhibition of ovarian secretion in preference to employing a hormone antagonist were the first to use oestrogen for the treatment of breast cancer in women This treatment was confirmed by Nathanson (1947) who found it to be effective in post menopausal women suffering from this disease Pearson (1955) in a recent review claims remission in 45 per cent of cases

Let us now investigate some of the experimental evidence upon which some of this work we have briefly discussed is based It is proposed to discuss the induction of tumours of the prostate kidney pituitary testes and ovary (see Figure 1) and also in some instances their prevention by using an appropriate hormone antagonist These tumours have been purposely selected because in some instances both their induction and behaviour are anomalous

Carcinoma of the Prostate Gland

There is no doubt that an endocrine dysfunction is an etiological factor in the cause of prostatic cancer in man, for it has been shown that tumours of the prostate can arise by an alteration of the hormonal environment

In man the growth of most tumours of the prostate can be held in check for considerable periods by the adoption of anti androgenic measures, as Huggins and Hodges (1941) have admirably shown The induction, however, of prostatic tumours in rodents and even in many higher animals constitutes an anomaly, for so far there have been no successful attempts to produce malignant prostatic cancer in these animals by the administration of hormonal agents A glandular carcinoma of the prostate, however, was produced by Horning (1946), not by hormonal administration but by treatment with one of the carcinogenic hydrocarbons, namely 20 methyl cholanthrene Slices of mouse prostate, which had been carefully wrapped around crystals of this compound, were implanted subcutaneously into host mice of the same strain Some of the prostatic tumours which subsequently developed were glandular cell carcinomas, but most were of the squamous cell variety It was found that the glandular cancers could all be successfully grafted into intact mice but could not all be successfully grown in host mice castrated before puberty Some of these tumours would grow in castrated mice providing the host animals were treated with testosterone propionate Later it was found that those tumours which were dependent upon the male sex hormone for their sustained growth as grafts were glandular cell carcinomas, whereas the prostatic tumours which had become hormone independent and were growing as autonomous lesions had recently undergone squamous metaplasia during serial transplantation The glandular cell tumours were hormone sensitive but once they had undergone squamous metaplasia they became androgen independent These experiments are of interest for two reasons First because it was found possible to induce a hormone dependent tumour in a gland under endocrine control with a carcinogenic hydrocarbon without the direct intervention of a hormonal agent Secondly,

because once the chemical constitution of the prostatic cancer cell had altered, it ceased to be dependent on the male sex hormone for its sustained growth This is in fact, to use the terminology of Furth, an example of an autonomous variant

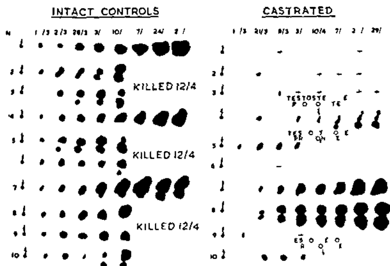


Fig 2 Silhouette chart showing dependence of transplantable prostatic mouse carcinoma on androgens

Here is an endocrine dependent tumour becoming independent of hormonal modification once it had undergone a spontaneous cellular differentiation (see Figure 2) Special emphasis has been laid on this mouse prostate work not merely because it constitutes an anomaly in endocrine carcinogenesis but also because this work has recently been confirmed and extended by Dr Mirand (1955) of the Memorial Institute at Buffalo

Renal Neoplasia Induced by Oestrogens

Let us now pass on to the induction of kidney tumours by oestrogen administration in the male golden hamster One of the most interesting findings in the field of endocrine carcinogenesis was made originally by Kirkman and Bacon (1949) of Stanford University They found that prolonged treatment with naturally occurring or synthetic oestrogens induced kidney

neoplasia in the male but not in the intact female hamster This work has been confirmed and extended by Horning and Whittick (1954) The several interesting problems which this investigation has brought to light are not yet fully appreciated For instance, neoplasms in animals other than the hamster which are induced by hormones and are dependent upon them for their sustained growth, generally arise in organs of the body which either belong to the endocrine system or else come under the influence of the anterior pituitary gland Hamsters are the exception to this rule in that the kidney, except as a part of the body subject to the general stimulation of somatotrophin, is not directly influenced by the pars anterior

These oestrogen induced kidney tumours possess all the histological characteristics of malignant lesions They arise in the cortex in association with either the distal or proximal tubules, and later invade the medulla and the renal pelvis They also metastasise Secondaries are seen in the body cavity as well as in the lung and liver

Another anomaly is that prolonged treatment with oestrogens invariably produces pituitary tumours of the pars intermedia, whereas in other rodents similar treatment induces chromophobe lesions of the anterior lobe

Absorption Rates of Implanted Pellets

The differences in absorption rate between stilboestrol pellets implanted subcutaneously in the hamster desert rat and albino rat are illustrated in Figure 3 The absorption rate of the hamster is slower than in the other two rodents and this might explain why hamsters are able to tolerate such large amounts of stilboestrol

It will be seen in Figure 3 that a deflection in the absorption rate of the tablets in each of the three rodents occurs on approximately the fourteenth day after subcutaneous implantation at a period when the pellets become encapsulated Cowie and Folley (1945) contend that this falling off is due solely to a sudden decrease in the surface area of the pellets

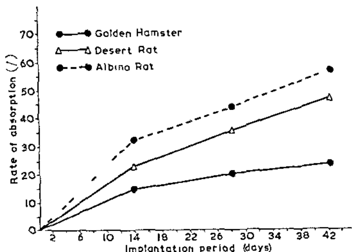


FIG 3 Absorption of stilboestrol in golden hamster desert rat and albino rat

HORMONAL FACTORS DETERMINING SUCCESSFUL TRANSPLANTATION

Many unsuccessful attempts have been made to transplant these induced primary kidney tumours into hamsters of both sexes and of varying ages The failure of these kidney tumours to grow either as subcutaneous or intraperitoneal grafts was surprising as they possessed all the histological criteria of malignant lesions

Consideration was then given to the fact that as the neoplasms are dependent upon high levels of oestrogen for their induction they might also be dependent upon the continued presence of this hormone in excessive amounts for their maintenance as grafts After a long latent period the grafts grew only in oestrogen pre treated hosts

One of the most interesting features is the long latent period which exists between tumour transplantation and the appearance of palpable lesions A tumour now in its eighth generation of serial transplantation is seen in the following histogram (see Figure 4) It will be noticed that the duration of the latent period between transplantation and the appearance of a palpable lesion shows a marked decline in each successive serial graft

Even although this kidney tumour has been grafted for several years and the latent period has been reduced from nearly twelve months to four weeks, before palpable lesions develop this tumour still retains its dependency upon oestrogen for

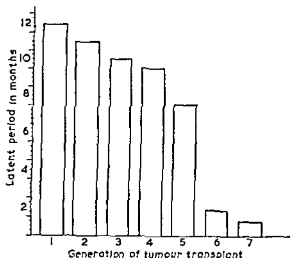


FIG 4 Histogram showing decline in latent period preceding growth of graft

maintenance as a graft If transplanted into untreated hamsters the tumour will no longer grow

These oestrogen induced grafted kidney tumours conform in their behaviour with many other types of hormone dependent transplantable tumours observed in laboratory animals Experiments were therefore undertaken and are still in progress, to determine whether or not these primary transplantable tumours are capable of growing following abrupt withdrawal of the hormonal stimulus Removal of the stilboestrol pellet from the subcutaneous tissues is easily achieved and is followed by a gradual regression of the primary tumours The regression is particularly easy to follow in grafts which have been implanted in the tail of host hamsters The effect of this withdrawal upon the secondary and transplanted lesions is still under consideration As these kidney tumours are hormone dependent for their sustained growth experiments were also undertaken to

determine if tumour formation could be prevented by simultaneous treatment of the host with stilboestrol and its antagonist, testosterone propionate If renal neoplasia could be prevented by this means, this would be additional evidence of the endocrine nature of tumours arising in a gland which is not under the direct influence of the endocrine system

PREVENTION OF STILBOESTROL INDUCED RENAL TUMOURS WITH TESTOSTERONE PROPIONATE

The set up of this experiment was simple Sixty male hamsters all twelve weeks of age were divided into three separate groups each consisting of twenty animals The first group were treated with stilboestrol alone the second received combined treatment with stilboestrol and testosterone propionate and the third group were untreated

Examination of Table 1 shows that with the exception of one all the stilboestrol treated hamsters developed palpable kidney tumours at various intervals up to ten to eleven months after the commencement of treatment All these renal lesions were bilateral and multifocal and varied considerably in size The size of the growth does not always depend upon the duration of treatment For instance the single hamster in this group which developed no palpable tumour at the end of this period of treatment was found at post mortem to possess naked eye cortical lesions in each kidney None of the hamsters receiving the combined treatment with stilboestrol and testosterone developed any kidney tumours (see Table 1) The testes and seminal vesicles in contrast to those treated with stilboestrol alone showed no atrophic changes It will also be noticed that no spontaneous kidney tumours appeared in the group of animals which received no treatment (see Table 1)

These experiments with a hormone antagonist demonstrating conclusively that kidney tumours in the hamster can be prevented by combined treatment with stilboestrol and testosterone provide additional evidence that renal neoplasia in the hamster comes under the category of hormonal cancer

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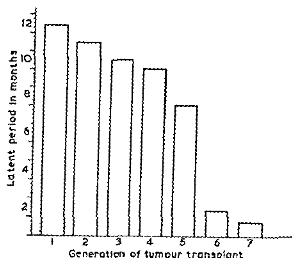


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Ever since Price in 1941 by grafting the ovaries of rats on to the ears of litter mates demonstrated that the difference in temperature stimulated the secretion of androgens instead of oestrogen, it has been shown that under certain conditions a reversal of sex hormone secretion can also occur in the testis Bielschowsky (1954), in an ingenious experiment on induced cryptorchidism in rats, has demonstrated that the interstitial cell stimulating hormone of the pituitary leads to a hyperplasia of the Leydig cells of the testis which are normally associated with the secretion of androgen but which do under these conditions elaborate oestrogens in sufficient amounts to induce proliferation of the mammary epithelium in the operated hosts These results of Bielschowsky are of interest when examining the testes of men with breast cancer There are indications that these breast tumours may have developed as a result of a hormonal imbalance Frozen sections were cut off the testes after they were imbedded in gelatine They were then stained with Sudan IV

The cells of the adrenal cortex, the theca interna off the ovary, and the interstitial cells of the testis all contain lipids in their cytoplasm which are associated with the formation and storage of steroid hormones A large part of the lipid is in the form of cholesterol which gives a positive reaction to the Lieberman Burchardt test Fat soluble dyes like the Sudan series stain the total lipid and naturally do not distinguish between specific steroids Cytological examination of these human testes from men with breast cancer showed abnormal increase in the number of the Sertoli cells in the seminiferous tubules and a marked proliferation of the Leydig cell tissue Whether or not the abnormal amounts of steroid hormones elaborated by the testes in these instances initiated breast cancer and can be regarded, as Dr Furth would say, as the intrinsic agent in the etiology of the disease can only be regarded as a matter of speculation It does however warrant further examination

Discussion

Let us briefly review some of the anomalies we have encountered in the induction of tumours of the ovary prostate and kidney

TABLE 1 Prevention of stilboestrol induced renal tumours in the male golden hamster with testosterone propionate

No of hamsters	Form of treatment	Duration of treatment	Results
20♂	Stilboestrol alone (20 mg pellets)	10½ months	18 palpable renal carcinomas 2 early cortical tumours (not palpable)
20♂	Stilboestrol + testosterone propionate (20 mg stilboestrol) (2 5 mg weekly in oil)	16 months	No renal tumours developed 1 hamster developed a unilateral hydronephrosis
20♂	No treatment	16 months	No spontaneous kidney tumours

INDUCED OVARIAN TUMOURS

We shall now pass on to another anomaly in endocrine cancer This deals with the induction of ovarian tumours following regular administration of the male sex hormone commencing 48 hours after birth

These ovarian tumours were all theca cell lesions and were induced in albino rats eighteen months after the commencement of treatment These tumours are of interest for two reasons, first because the ovary itself is a target organ of the endocrine system, and second, because testosterone has never been seriously regarded as a potential carcinogenic agent, although Lacassagne (1939) had claimed that repeated inoculations with the male sex hormone, under strictly controlled conditions, induce subcutaneous sarcoma

HORMONAL IMBALANCE IN MAN

I pass now to the possible association of breast cancer in man with a spontaneous hormonal imbalance It is established that in women the ovary although not the sole source of oestrogen in the body, plays an important role in the etiology of mammary cancer Huggins and Moulder in 1945 were the first to demonstrate that the Sertoli cells in the testis of the dog produced oestrogenic hormones

organ which is strictly not a member of the endocrine system and moreover does not come under the direct control of the anterior lobe of the pituitary gland Furthermore these kidney tumours are hormone dependent lesions since the tumours regress following abrupt withdrawal of the hormonal stimulus even although they are capable of metastasising via the lymphatic pathway The induction of kidney tumours in the hamster is an interesting exception to the general rule since other species of rodents after similar treatment never develop renal carcinoma Preliminary experiments still in progress suggest that the liver of the hamster differs from that of the rat, mouse and guinea pig in that it is unable to cope adequately with the inactivation of oestrogens Also other experiments have demonstrated that the renal epithelium of the hamster is endowed with a peculiar susceptibility to renal neoplasia The results obtained with stilboestrol suggested the possibility that kidney cancer in the hamster might possibly be due partly to absorbed chemical carcinogens acting selectively on the renal epithelium during excretion This contention was strengthened by the fact that kidney tumours could be induced in the hamster by subcutaneous injection at a remote site with 3 4 benzpyrene, while none developed in albino rats following similar treatment It was of further interest to record that this particular carcinogenic hydrocarbon has been shown by Cook and Dodds (1933) to possess oestrogenic activity

Another peculiarity about the hamster is the development of tumours of the pars intermedia, whereas other rodents following oestrogen treatment only develop chromophobic lesions of the anterior lobe of the pituitary Taking into account this unique response of the hamster pituitary to oestrogen treatment experiments are being undertaken to determine whether kidney tumours could develop in the absence of a functioning pituitary Necrosis of the pituitary gland in normal untreated hamsters is produced by inserting radio active seeds into the hypophysis via the trans nasal route This should determine whether the action of oestrogen in the hamster is a direct or an indirect effect This would yield additional information on the mechanism of renal tumourigenesis in these animals

before discussing the general problems of endocrine carcino genesis

The production of ovarian tumours in the albino rat following massive doses of testosterone propionate was first observed by the late Mr Harold Burrows some years ago at the Chester Beatty Research Institute Recently I confirmed his contention The neoplasms were all theca cell tumours The histogenesis of these lesions is obscure, but many workers regard them, and I believe quite rightly, as endocrine lesions arising from the stromal cells of the ovarian cortex The results were surprising not only because the ovary is a target organ of the endocrine system, but also because testosterone has never seriously been regarded as a potential carcinogen What then is the rationale?

When I discussed these unpublished results at the last Gordon Conference in New London Dr Engel (1955) said he was not surprised since he had recently discovered that testosterone was converted in the body into oestradiol Pearson, working at the Sloan Kettering Institute, New York, contends that androgen sometimes accelerates the growth of mammary cancer in women, which he attributes to the possible conversion of androgen into oestrogen The reason why progesterone occasionally stimulates instead of inhibits tumour growth in women might likewise be due to the same cause

In view of these results, the recent work of van Eck and Chang (1955) is of direct interest They found that ovarian tumours in rodents develop more readily in testosterone treated X rayed mice than they do in X rayed animals which have not been treated with male sex hormone When considering that after injection androgen might possibly be converted into oestrogen, the known capacity of the gonadal hormones to stimulate mitoses of fibrocytes should also be taken into con sideration

If this conversion does occur in vivo, then it should be possible to induce renal neoplasia in the hamster by prolonged treatment with the male sex hormone alone These experiments are already in progress

We have also seen in the case of the hamster that continuous administration of oestrogen can induce kidney carcinoma in an

tumours in mice by treatment with a carcinogenic hydrocarbon alone without the direct application of a hormonal agent, as we have just seen constitutes an anomaly, some information of interest was brought to light regarding the factors regulating the behaviour of the malignant cancer cell to the male sex hormone As long as the prostatic tumour cells remains a glandular cell carcinoma it is hormone dependent, but as soon as it undergoes squamous differentiation it ceases to be dependent upon andro gen for its sustained growth and immediately transforms into an autonomous lesion The question therefore arises Does the endocrine dependent cancer cell differ in its chemical compo sition from the autonomous malignant cell which has lost its responsiveness to the hormone restraining forces? In other words does this change from dependency to autonomy involve any fundamental change in cellular chemical patterns and meta bolism? Unfortunately these questions cannot be answered since the normal mechanism of hormone action is not yet fully understood It is thought that hormones constitute an important set of enzyme-regulating factors whose mode of action might be elucidated by the study of hormone enzyme relationships Nor as yet is anything known as to how a hormone acts in producing an abnormal cellular state

Until this problem is more fully appreciated it will be impos sible to comprehend the factors involved in inducing an endo crine dependent cancer to develop spontaneously into an unre strained growth or autonomous variant In the particular mouse prostatic carcinoma which I have mentioned the cancer cell before it metamorphoses from a hormone dependent into an autonomous lesion undergoes a pronounced cellular differen tiation and by histological examination it is therefore possible to predict beforehand the response of this tumour transplant to hormonal modification

Unfortunately this phenomenon is the exception to the rule Nevertheless it might provide suitable material when one endeavours to elucidate certain aspects of this fundamental pro blem The differences in the behaviour of endocrine and non endocrine dependent neoplasms are important when thinking in terms of chemotherapy It is not possible in other types of

One of the most fascinating features of endocrine tumours is their dependence upon a particular hormone, and the dramatic manner in which many regress once the hormonal stimulus is withdrawn In the case of renal neoplasia in the male hamster we find that changes produced by oestrogen are reversible and last only as long as oestrogen is available to maintain the tumour Another feature of interest in hormone dependent transplantable tumours in laboratory animals is the long latent period which exists between implantation and the development of palpable lesions As we have seen the latent period is gradu ally reduced during each successive serial generation of trans plants These renal tumours are now in their eighth serial generation, and are still hormone dependent since they will not as yet grow in non oestrogenized hosts This is of exceptional interest, as there is a tendency for most endocrine dependent neoplasms growing in experimental animals gradually to lose their dependence upon a particular hormone after they have been transplanted for several generations There are only a few exceptions to this rule Muhlbock (1954) in Amsterdam induced a rodent ovarian tumour by administration of pituitary gonado trophins This particular tumour is now in its fourth year of serial grafts and is still dependent upon either androgens or oestrogens for its maintenance There are no indications that it will develop into an autonomous variant

The question naturally arises as to whether the oestrogen acts directly on the tumour cell of the graft or whether the hormone brings about changes in the pituitary gland which in turn indirectly stimulate the latent tumour cell into its malignant phase The long periods in which these tumour cells remain quiescent as subcutaneous grafts suggests that the pituitary might possibly be involved In view of this, normal untreated male hamsters are now receiving transplants of pituitary tumours prior to the implantation of kidney carcinoma grafts If these renal grafts will grow in non oestrogenized hosts bearing pituitary tumour implants it would give valuable information on the biological mechanism controlling the behaviour of hormone dependency

Although the induction of hormone dependent prostatic

Data is now accumulating on the effects of hypophysectomy on patients suffering from breast cancer Some of these reports deal with patients having disseminated carcinoma who have had an adrenalectomy but have suffered a relapse after varying periods of remission In the last resort a hypophysectomy has been done In several of these cases a further rapid regression of the carcinoma has been obtained In others in which reactivation of the growth had occurred, following gonadectomy and adrenalectomy post mortem examination has revealed the presence of accessory cortical adrenal rests These were apparently the cause of the reactivation of the growth Recurrences of this kind after a remission in the absence of ovaries and adrenal glands suggests that the anterior pituitary in attempting to maintain an equilibrium is capable of stimulating the hypertrophied adrenal rests to secrete oestrogen in sufficient amounts to reactivate the quiescent neoplasm Pearson contends that there is also evidence suggesting that the reoccurrence of some breast carcinomas is due to a pituitary hormone or hormones acting in addition to oestrogen Indeed, accessory cortical tissue is not always found in cases which have undergone reactivation One wonders whether prolactin acting alone or in combination with other pituitary hormones will not eventually be found to play an important role in this complicated story

Remission of endocrine cancer whether obtained by a hormone antagonist or by depression of pituitary function by oestrogens or by surgical removal of the gonads and adrenals is only temporary in duration Sir Stanford Cade (1955) in a recent review of one hundred cases states that remission following adrenalectomy and maintenance on cortisone varies from several months to three years Huggins of Chicago who initiated this form of surgical therapy claims remissions in some instances up to six years

There are many gaps in our knowledge and perhaps more concentrated study of some of the anomalies in endocrine carcinogenesis will help in the final solution of this problem The fact that some types of endocrine cancer can in many instances be fully or partly controlled by an alteration of the hormonal environment of the host is to say the least encouraging

known tumours either in animals or in man to ascertain by histological methods whether a particular tumour is hormone dependent or not Huggins, however, does contend that any breast cancer which has undergone anaplastic changes is invariably more resistant to hormone therapy

Ever since Huggins and Scott in 1945 first used gonadectomy combined with bilateral adrenalectomy for controlling the growth of breast and prostatic cancer in man many attempts have been made to find some method by which it would be possible to predict before operation whether the tumour was a hormone dependent lesion A promising step has been made recently by Pearson (1955) and his co workers in New York They found that measurements of urinary calcium excretion in men with prostatic cancer revealed the existence of two kinds of osteolytic metastases one dependent on oestrogen and the other non dependent It is the former type of patient who responds to adrenalectomy which reduces oestrogen production and thus brings about a remission of tumour growth Additional investigations may well confirm these findings and establish the value of urinary calcium determinations as a guide to the form of therapy to be taken in prostatic and breast cancer

Recently Hadfield (1956) has also been studying methods by which it is hoped to determine beforehand whether or not patients with breast cancer possess hormone dependent tumours This author is of the opinion that breast tumours are more likely to regress when the production of oestrogen is diminished and the output of gonadotrophin in the urine is increased He claims to have identified a mammatrophic factor from human urine This factor has no oestrogenic activity, and it is not apparently found in the urine after hypophysectomy Hadfield admits that the mammatrophic substance present in human urine is probably prolactin It is known that the prolactin content of urine goes up during parturition and it will be necessary to distinguish between prolactin urinary output occurring normally at various times and ages from that which they claim to be indicative of breast cancer If these tests can be made truly reliable for the clinical detection of hormone dependent breast cancer treatment by hypophysectomy would be established on a firmer basis

XXV

Recovery from the Lethal Effects of Radiation[1]

J F LOUTIT

In the last ten years protection against ionizing radiation has become a matter of very considerable importance Formerly it was a matter of concern only to those few who were routinely exposed to radiation The radiation was from X rays in medical diagnosis and therapy and in industrial radiography from gamma rays in similar occupations and in the then limited academic fields of radio chemistry and nuclear physics Since the discovery of nuclear fission however, occupations necessitating exposure to ionizing radiation are increasing daily and will continue to involve more and more people Permissible daily or weekly doses of the various kinds of radiation have been assessed but apart from routine, there is always the prospect of accident in which considerably greater doses may be received

Routine protection now as heretofore is a matter of prophylaxis Sources of radiation must be surrounded with shielding material such as lead or concrete which must physically prevent the radiation from reaching the operative Internal contamination of the body with radioactive materials must be prevented by a most scrupulous attention to detail of laboratory and industrial technique But in accidents—or for that matter of fact in nuclear warfare—these conditions do not obtain and men may receive serious over dosage For the physician this poses the problem, Can the body be conditioned against the effects of

[1] An earlier version of this paper was presented at the Radiation Biology Symposium Melbourne December 1955

Let me conclude as I begin by quoting a pertinent remark by Dr Jacob Furth 'Recognition and adjustment of the hormonal disturbance in this disease is in fact cancer prophylaxis'

REFERENCES

BIELSCHOWSKY, F (1954) *Proc Univ Otago* 33 16
CADE SIR S (1955) *Brit med J* I, 1
COOK, J W and DODDS SIR E C (1955) *Nature* 31 205
COWIE A T and FOLLEY S J (1945) *J Endocrinol* 4 375
CRAMER, W and HORNING, E S (1938) *Lancet* Jan 8, 72
ECK VAN V and CHANG C H (1955) *Cancer Res* 15 280
ENGEL L L (1955) Personal communication
FURTH JACOB (1955) *Recent progress in Hormone Research*, p 221 Academic Press New York
HADDOW, A WATKINSON, J M and PATTERSON, E (1944) *Brit med J* II 393
HADFIELD G (1956) *Brit med J* I 94
HORNING E S (1946) *Lancet* Dec 7, 829
HORNING, E S and WHITTICK J W (1954) *Brit J Cancer* 8 451
HUGGINS C and HODGES C V (1941) *Cancer Res* 1, 293
HUGGINS C and MOULDER P H (1945) *Cancer Res* 5 510
HUGGINS C and SCOTT W W (1945) *Ann Surg* 122 1031
KIRKMAN H and BACON (1949) *Anat Rec* 103 475
LACASSAGNE, A (1932) *Compt rend Acad Sci* 195 630
LACASSAGNE A (1937) *Compt rend Soc Biol* 126 190 and 385
LACASSAGNE A (1939) *Compt rend Soc Biol* 132, 365
LOESER A (1940) *Brit med J* I 479
MIRAND, E A (1955) Personal communication
MUHLBOCK O (1954) Congres international de Gynecologie et d Obstétrique Geneva
NATHANSON I T and ANDERVONT H B (1939) *Proc Soc exp Biol and Med* 40 421
NATHANSON I T (1947) *Endocrine Aspects of Cancer* p 26 Academic Press, New York
PEARSON O H WEST C O and HOLLANDER V P (1954) *J Amer med Ass* 158 234
PEARSON O H (1955) *J Amer med Ass* 159 1701

a lethal dose of X rays This hypothesis seemed to be strongly confirmed by work from the National Cancer Institute at Bethesda Egon Lorenz and his colleagues (Lorenz Congdon and Uphoff, 1952) showed that not only was normal spleen effective in therapy, but normal bone marrow was equally good Jacobson had implanted normal spleens intraperitoneally Bone marrow is not a discrete organ like spleen but a diffuse tissue Lorenz, therefore, injected suspensions of bone marrow intraperitoneally and later intravenously with even better results This was a considerable technical gain Moreover Lorenz made the notable discovery that therapeutic potency was not confined to normal mouse bone marrow but that normal guinea pig bone marrow would also serve though larger doses were necessary This seemed to identify the active principle as a chemical agent The alternative hypothesis to chemical stimulation of the damaged marrow would be colonization of the affected marrow by normal cells from the injection or the implant and regrowth of marrow from the seeded cells However it is an axiom supported with much experimental evidence that transfer and growth of cells from one species of normal animal to another does not occur It is barred on immunological grounds Such heterografts even if they do take initially are soon rapidly thrown off as the recipient develops an immune reaction which destroys the graft Therefore, in this case seeding or colonization seemed to be ruled out and a chemical agent favoured Furthermore in San Francisco Cole and his colleagues at the Naval Radiological Defence Laboratory (Cole Fishler and Bond 1953) began to refine the suspensions which they used for injection In the first place the tissues were subjected to more severe treatment than is required simply to make a suspension They were ground in a Potter Elvejhem homogenizer with a special medium and such homogenates were proved active Separation of the various fractions of the homogenate by ultracentrifugation showed that the mitochondrial and microsomal fractions of the cells were without effect but the nuclear fraction was the potent one

Our own work at the Radiobiological Research Unit at Harwell (Barnes and Loutit 1953) began after Jacobson s

over exposure or if over exposure has occurred can treatment alter the subsequent chain of biological events?

For the purposes of this discussion we will consider only over exposure to external radiation and only over exposure to X or gamma radiation Also, while considerable investigation has been carried out on prophylactic measures through chemical means no method which yet gives promise of practical application has been uncovered Therefore, we will consider only recent advances in potential therapy

Injection of Haemopoietic Tissue

From the viewpoint of experimental medicine the first real progress in this field was made by Leon Jacobson and his colleagues in Chicago (Jacobson, 1952) Jacobson had observed that mice given penetrating X rays to the whole body died with aplastic anaemia after a certain critical measured dose Presumably the dose of radiation given to the bone marrow was not greatly different from the dose recorded in air On the other hand, mice given injections of radioactive strontium which localizes most strongly in the bones, whence the beta rays irradiate the marrow, need a much larger calculated dose of radiation in the bone marrow to cause death from aplastic anaemia It, therefore, occurred to Jacobson that the spleen of mice, not irradiated to any great extent by radiostrontium but irradiated along with the rest of the body by X rays might be exerting a protective effect in the former case In support of this thesis was his experiment wherein mice were totally irradiated with X rays except for the spleen which was shielded by lead This approximately doubled the dose of X rays necessary to kill the mouse Later it was shown that a similar experimental result could be obtained by irradiating the mouse totally but in addition treating the mouse subsequently with an implant of spleen from normal mice To Jacobson this signified that the normal mouse spleen—either protected from the X rays given to the rest of the whole body or administered therapeutically after total irradiation—contained a humoral agent which caused accelerated recovery of the damaged bone marrow and allowed the mouse to survive what otherwise would have been

poorer results and below that usually no result The minimal effective dose is about 10^6 nucleated cells (Others have reported even lower effective doses) Similar suspensions from spleens of strain A mice give comparable survival at 30 days However, if the mice are not then killed, for histological purposes or because of shortage of accommodation as is so often the case, but are allowed to live till spontaneous death a difference between the groups given isologous and homologous material is readily observed Our unirradiated CBA mice have a median life span of about 900 days, those irradiated at the age of about 100 days and treated with isologous spleen live for a median period of 500 days longer, whereas those irradiated at 100 days and treated with homologous spleen live only a few months longer (Barnes and Loutit, 1955b) We have not investigated the cause of this death It could be explained on the cellular theory as follows Normally mice will not tolerate a homograft any more than a heterograft for more than about ten days By this time they begin to develop an immune reaction against the foreign antigens and the reaction of antibody with antigen results in death of the cells carrying the antigen However, the capacity of the mammal to form immune antibodies is impaired after massive doses of radiation It is possible to conceive that the mouse tolerates a homograft for longer than normal and only recovers its ability to form the appropriate antibody after some weeks or months or even longer when it does recover this faculty, the graft is belatedly destroyed Transposing the hypothesis to the irradiated CBA mouse one could postulate that myeloid spleen cells of strain A mice colonize and grow in the CBA mouse and form a significant part of the recovered mouse s bone marrow but, when the reaction of immunity is restored to the CBA mouse it develops antibodies against A cells which destroy much or all of its effective A marrow It is also possible to postulate an opposite view The myeloid A tissue from the donor grows and gradually differentiates not only into mature red and white blood cells but also into reticulo endothelial tissue with the capacity to form antibodies This donor tissue therefore can in theory form antibodies against the host and kill it

preliminary report and when his humoral theory seemed most likely However, our attempts to prepare active extracts of spleen from mice and other mammals were fruitless and this is the experience of every other worker who has tried It was observed that the intraperitoneally implanted spleens appeared to 'take' and survive We returned, therefore, to first principles to rule out the celullar hypothesis of seeding We confirmed that suspensions were in practice more effective and more easily administered and that the intravenous route was superior to the intraperitoneal This was difficult to explain on the humoral theory but in accord with expectation if seeding were taking place

The agent in spleen or bone marrow is extremely thermolabile It is destroyed in a few hours at room temperature and is not preserved at 4° C or −15 C, the usual conditions of storage for unstable biological agents We (Barnes and Loutit 1955a) have shown however, that it is preserved by a technique of storage in glycerol at low temperatures which has become standard for preservation of whole cells

Originally we could not make our mice of the inbred CBA strain recover with suspensions of spleen or bone marrow from guinea pigs or rabbits Heterologous material from foreign species having been ineffective, we turned our attention more to homologous material from different strains of mice Tissue from mice of the same in bred strain should be genetically and anti genically identical (isologous), tissue from mice of different strains is genetically and antigenically more or less different (homologous) The CBA mouse was always used as the irradiated subject 950r X rays (240 kv, 15 ma, HVL = 1 2 mm Cu 43r/min) has been virtually 100 per cent lethal to these animals untreated If they are given intravenous injections of suspensions of spleen cells from infant CBA mice a satisfactory percentage recover and survive the conventional 30 day period post radiation Too great a mass of material injected is immediately fatal presumably from embolism but suspensions made from four infant spleens (about 100 mg) in 0 4 ml of normal rabbit serum are usually tolerated Suspensions of 1/10th of a spleen give equally good results, 1/20th of a spleen definitely

response within a few days If the animals were not immune the tumour would grow for about ten days and only then regress The test animals were thus killed ten days after a subcutaneous injection of Sarcoma 1 given ten days after their test injection of tissue or tissue fluid The results indicated that spleen, lymph glands and induced peritoneal exudates in the irradiated CBA mice treated with A spleen contained A antigen for at least seven weeks Normal unirradiated CBA mice injected intra venously with suspensions of A spleen contained A antigen for at the most one week only In a second set of experiments CBA mice given sublethal doses of 500r were given suspensions of spleen from A mice immunized against *B typhosus H* antigen The irradiated mice were found to develop agglutinating anti bodies against *B typhosus* which increased with time, indicating the survival and function of the donated material

We believe that, though all the foregoing results could be accounted for by the transference of a chemical antigen from the donor and its adoption by the host in a manner akin to bacterial transformation the true explanation is colonization of the host by seeded cells The most convincing evidence for this is from our most recent and still incomplete work

We have noted that originally we were unable to obtain sur vival from heterologous tissue However following Congdon and Lorenz (1954) we have confirmed that rat bone marrow, from our inbred strain of albino rat of Wistar origin, will give some survival of the irradiated CBA mouse The tissues of such surviving mice have been examined cytologically by our col leagues Ford and Hamerton (Ford, Hamerton, Barnes and Loutit 1956) The animals previously injected with colchicine are killed, suspensions are made of bone marrow spleen, lymph glands and thymus, and the materials are prepared by a modi fied Feulgen squash method Cells in the metaphase of mitosis are then examined The chromosomes of the rat differ in appearance and number from those of the mouse In these recovering tissues virtually all the cells in metaphase correspond with the picture characteristic of the rat Similarly it has been shown that the same holds when homologous tissue is trans ferred The donor mouse in this case is a mouse carrying a

Also in favour of the seeding hypothesis is our other observation using homologous material We have already noted that suspensions of spleen of strain A mice prolong the survival of *some CBA mice, which have been given the supralethal dose of* 950r, beyond the normal period of scoring namely 30 days However, if the CBA mice had been previously exposed to the A antigen this result was not obtained The mice died within ten days of the 950r in a fashion comparable with untreated controls (Barnes and Loutit, 1954) This suggested that the previous administration of the A antigen had resulted in immunity to A cells, so that A material given as therapy was destroyed before it could be effective We have since shown that there is certainly an immunity in so far as an anti A haemagglutinin can be demonstrated in the circulating blood (Barnes and Loutit, 1956)

Still further favouring the seeding theory is the result of Main and Prehn's experiment (Main and Prehn 1955) Mice of strain DBA/2JN were given the lethal dose of radiation and treated successfully with isologous material Thirty days later they were grafted with skin from homologous mice of strain BALB/cAnN In 2 instances out of 31 the skin graft took Still more important, when similar DBA mice were given as therapy material from the F_1, DBA/2JN × BALB/cAnN mice, and were grafted 30 days later with BALB/cAnN skin, 33 out of 36 grafts 'took

Mitchison (1956) working in our laboratory has adduced further evidence derived from immunological experiments that, with our practice of using cells of strain A as homologous therapy for CBA mice, the A antigen persists and increases in CBA host s haemopoietic tissue

The methods used for this demonstration were ingenious In one set of experiments tissues and tissue fluid were taken from the treated animals killed at various times after treatment They were made into suspensions (if not already fluid) and injected into normal CBA mice which became the test animals If the injected material contained A antigen in any significant quantity, it would produce a state of immunity within about ten days In this state a graft of tumour specific for the A strain, Sarcoma 1, would be rejected by the so called second set

CHEMICAL PROTECTION

It would appear that this colonization is effective not only in the unpremedicated mouse lethally irradiated but also in the chemically premedicated Originally Jacobson had claimed that spleen' protection and chemical protection with cysteine were not additive This suggested that both acted similarly by stimulation of the damaged animal s stem cells to divide and differentiate Recently, however at Oak Ridge Hollaender and Stapleton (1955) have shown that premedication with β aminoethyl thiouronium Br HBr and post medication with spleen allow recovery of some mice from doses as high as 2,400r of γ rays This suggests that the chemical protection reduces the biological effect of the radiation to one half or less of that in the unprotected animal and that the therapy allows recovery from the effective 1,200r more or less

SUMMARY

These dramatic results are of considerable interest in fundamental radiobiology They still, however are of little moment to the clinician If our interpretation is correct this form of therapy cannot be applied to man It is conceivable that one could collect human haemopoietic tissue and store it for considerable periods in cold glycerol But man s antigenic formula is infinitely variable The donated haemopoietic tissue might grow in the irradiated human subject and recolonize the damaged marrow but the antigenic differences would result sooner or later in an immune response characteristic of the homograft The irradiated human might have an acquired tolerance of the graft due to his over exposure to irradiation but one is still left with the problem of making the graft tolerant of the host whilst retaining the capacity to react against bacteria viruses and toxins

REFERENCES

BARNES D W H and LOUTIT J F (1953) *Proc Roy Soc Med* 46 251
BARNES D W H and LOUTIT J F (1954) *Nucleonics* 12 No 5 68
BARNES D W H and LOUTIT J F (1955a) *J Nat Cancer Inst* 15 901

also impairs the power of the animal to repair the damage In the untreated animal it is this inability to recover sufficiently early which results in its death When normal haemopoietic tissue is injected intravenously, living cells are transferred by the circulation to the usual sites of haemopoiesis where they settle down, colonize the tissues and function By the end of a week or ten days they are usually sufficiently productive to tide the animal over the time when death would otherwise supervene The fact that homologous or even heterologous tissue is able to do this indicates that the normal mechanisms of immunity are gravely upset by the unduly heavy dose of radiation The animal from the aspect of immunity is in a state similar to the embryonic it has acquired tolerance for foreign tissue This surviving graft can produce not only circulating cells and particles but also soluble substances, antibodies, etc which maintain the defences against bacterial invasion In animals which have died in spite of treatment and have been sufficiently fresh to be worth histological examination we have not found the evidence usually attributed to bacterial invasion With adequate defences against bacteria and their toxins the animals are protected temporarily against this form of death, as were the mice of others who were under cover from antibiotics If the graft produces cells and particles sufficiently easily and adequately, the animals are protected against death from anaemic anoxia—and from thrombopenia and its sequelae The closer the graft is antigenically to the host the more likely is it to produce cells which can function adequately The grafts must maintain function for a very long time—as instanced by the experiments of Main and Prehn—and production of antibodies by them against the host may well be the cause of the delayed death in the case of homologous and heterologous grafts We are impressed with this possibility from the very few results we have obtained in survival of F_1 mice—CBA × A—given A material The immediate recovery was good but the long term survival poor which would be expected from this hypothesis but not otherwise (chance excluded) as the A graft should be fully compatible from the host s point of view

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Barnes D W H and Loutit J F (1953) *Proc Roy Soc Med* 46 251
Barnes D W H and Loutit J F (1954) *Nucleonics* 12 No 5 68
Barnes D W H and Loutit J F (1955a) *J Nat Cancer Inst* 15 901

BARNES D W H and LOUTIT J F (1955b) In *Radiobiological Symposium* 1954 ed by Bacq and Alexander Butterworth London p 134
BARNES D W H and LOUTIT J F (1956) In *Progress in Radiobiology* ed Mitchell Holmes and Smith Oliver and Boyd Edinburgh p 291
CARTER T C, LYON M F and PHILLIPS R T C (1955) *J Genet* 53 154
COLE L J, FISHLER, M C and BOND V P (1953) *Proc Nat Acad Sci* 39 759
CONGDON C C and LORENZ E (1954) *Amer J Physiol* 176 297
CONGDON C C, UPHOFF D and LORENZ E (1952) *J Nat Cancer Inst* 13 73
FORD C E HAMERTON J L BARNES D W H and LOUTIT J F (1956) *Nature* 177 452
HOLLAENDER A. and STAPLETON G E (1956) Paper P/78 Proceedings of the Internat Conference on Peaceful Uses of Atomic Energy, United Nations New York, Vol 11 311
JACOBSON L O (1952) *Cancer Research* 12 315
LORENZ E CONGDON C C and UPHOFF D (1952) *Radiology* 58 863
MAIN J M and PREHN R T (1955) *J Nat Cancer Inst* 15 1023
MITCHISON N A (1956) *Brit J exp Path* 37 239

XXVI

Physiology of Nasal Circulation

DAVID SLOME

THE nose for all its anatomical prominence has been largely neglected by scientists investigating the physiology of the circulation The history of the development of our knowledge of the physiology of the nasal circulation shows brief periods of intense experimental interest alternating with long periods of apparently complete decline of interest

In ancient times Galen recognized the nose as essentially an organ of respiration and he was the first to appreciate that it served to heat the inspired air and so prevented cooling of the lungs In the seventeenth century the paranasal sinuses were almost the only part of the nose under investigation, while some believed that they contained air others were equally convinced that they were filled with animal spirits The scientific and experimental investigation of nasal functions began about 1850 However, in the later years of that century the emphasis shifted once more from function to structure Attention was directed to the shape and anthropological features of the nose which were described as revealing indicators of personal character, rather than to its internal architecture and functional activity At the beginning of the present century the work of Zwaardemaker and others again focused interest on nasal physiology

The first experimental demonstration of the nervous control of nasal blood vessels was carried out by Tschallusow in 1910 At this time the general pattern of the peripheral ganglia of the cranial autonomic had been substantially elucidated by Langley and others but the effects of electrical stimulation of these autonomic pathways on nasal blood vessels had not previously

been investigated In order to show changes in nasal vessels Tschallusow converted the nose into a closed chamber by blocking its anterior and posterior openings, and then recorded changes in volume of the nasal chamber with a tambour He studied the responses to stimulation of the nerves supplying the nose and also the reflex responses elicited by stimulation of afferent nerves in other parts of the body

In the period from 1920 to 1930 the effect of climatic conditions on nasal function was the main subject of experimental and clinical interest Yet once again that interest died away and apart from the important studies of ciliary motion by Proetz, Negus and Hilding and of the neurological aspects of olfaction by Adrian and by Allen, the nose as an object of experimental inquiry was neglected for twenty years

The vast array of experimental exploration in recent years of the physiology and pharmacology of the peripheral blood vessels has not been extended to embrace, to any appreciable extent, the nasal blood flow This is all the more surprising when we contemplate the great clinical interest in nasal vasomotor disease For recurrent and chronic nasal disorders such as vasomotor rhinitis constitute one of the most prevalent and most irksome of the minor afflictions of man, it has been estimated that during one week in February 1942, 20 per cent of the adult population of the United States of America were suffering from nasal vasomotor disorders and that nearly half of all man hours of work lost in factories in the war years in the United States of America was due to these nasal vasomotor disorders

Anatomy of Nasal Blood Supply

The nasal mucosa has an abundant blood supply from the sphenopalatine branches of the maxillary artery and from the anterior and posterior ethmoidal branches of the ophthalmic artery Zuckerkandl Swingle and more recently Dawes and Prichard have described the detailed architecture of the nasal vascular bed

The arteries lie in the depths of the tunica propria, arranged in parallel longitudinal rows From these vessels arterioles pass

towards the surface and supply subepithelial and periglandular capillary networks The efferent vessels from these capillary networks open into large irregular sinusoidal venous spaces The walls of these sinusoids are supported by abundant elastic tissue, and by circular and spirally arranged bundles of plain muscle The ends of the sinusoids are furnished with sphincter muscles and Lucas has demonstrated these sphincters in sections of human nasal mucosa Finally the blood drains from these sinusoids into deeper venous plexuses This vascular arrangement forms a type of erectile tissue and is especially well developed over the inferior turbinate and the lower margin and posterior end of the middle turbinate The corresponding parts of the septal mucosa are also highly vascular and erectile

The existence of arterio venous anastomoses in the nose had been claimed by Sucquet and by Harper Dawes and Prichard at Oxford used microdissection techniques on neoprene injected specimens and they provided for the first time detailed descriptions of the general pattern of distribution of nasal vessels in the common experimental animals They also demonstrated unequivocally that arterio venous anastomoses are present by passing the periglandular capillary system

Innervation of Nasal Vascular Bed

The control of the blood flow through the nose as of other organs and tissues, is regulated by both nervous and chemical mechanisms The vasomotor nerve supply is derived from both divisions of the autonomic nervous system (Figure 1)

The *sympathetic* preganglionic connector cells are presumed to be located in the lateral horn of grey matter in the first and second thoracic segments of the spinal cord This is inferred from knowledge of innervation of other cephalic structures There is as yet no experimental evidence substantiating this localization for preganglionic neurones innervating the nasal vessels

The preganglionic medullated axons emerge in the corresponding ventral nerve roots and traverse the mixed spinal nerves their anterior primary rami and white rami communicantes to the corresponding first and second thoracic ganglia of

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nerve These fibres pass through the vidian nerve and relay in the sphenopalatine ganglion Postganglionic fibres pass from the cells of this ganglion along its branches to the blood vessels and glands of the nasal mucosa

One aspect of the autonomic innervation of the nose remains obscure, i e to the region of distribution of the anterior ethmoidal nerve from the ophthalmic division of the trigeminal nerve Testut describes sympathetic fibres reaching this area from the superior cervical ganglion via the cavernous plexus and thence along the ophthalmic division of the fifth cranial nerve But parasympathetic fibres to this region have never been described

Experimental Study of Nasal Vessels

The principles underlying some of the methods used in the experimental study of nasal blood vessels are shown in the following table

TABLE I Methods used in investigating nasal blood flow changes

1 *Colour* of nasal mucosa inspection
    photoelectric plethysmography (Hertzman)
2 *Temperature* of nasal mucosa recorded by thermocouples
    (Mudd and Goldman)
    (Ralston and Kerr)
    (Richtner)
3 *Volume* changes (a) intranasal balloon
    (b) closed chamber technique (Tschallusow Jackson)
    (c) resistance to air flow
  Indirect Rhinometry
    Hygrometric method (Zwaardemaker)
    Rotating cylinder (Hellman)
  Direct Rhinometry
    (a) Volume of nasal air flow
      Movable vane or turbine in air stream
        (i) normal inspiration (Zwaardemaker Undritz)
        (ii) air sucked artificially through nasal chambers (Sternstein)
    (b) Pressure in nose recorded by water manometer
        (i) normal inspiration (Uddstromer Spiers)
        (ii) constant stream of air pumped into nose (van Dishoeck)
    (c) Velocity of nasal air stream (Blick Zwaardemaker Malan Worms)

Malcomson and I have recently reinvestigated the nervous control of these vessels and their responses to autonomic drugs

the sympathetic chain From here they ascend the cervical sympathetic chain to end by synapsing with cells in the superior cervical ganglion

From the superior cervical ganglion, postganglionic fibres might reach the nose by any of at least three routes

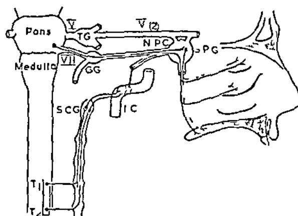


FIG 1 Diagram of autonomic innervation of nasal blood vessels

(1) From the cells of the superior cervical ganglion, axons pass to the plexus round the internal carotid artery and thence in the deep petrosal nerve to form part of the nerve of the pterygoid canal (vidian nerve) These post synaptic fibres then continue through the sphenopalatine ganglion without relaying, to be distributed with the branches of that ganglion to the nasal mucous membrane Experimental evidence that this is the path way of postganglionic fibres in the cat will be presented

(2) Blier, on the other hand, has contended that in the dog only a minor part of these postganglionic fibres pass through the sphenopalatine ganglion, the major group passing along the second division of the trigeminal nerve and its sensory branches to the nose

(3) Others have claimed that the postganglionic sympathetic fibres pass with the blood vessels as extensions from the plexus round the external carotid artery and its branches

The *parasympathetic* supply is by preganglionic fibres in the facial nerve which course along the greater superficial petrosal

I have mentioned that the course of the postganglionic fibres is disputed In the cat it can be shown that they pass almost exclusively via the deep petrosal nerve through the sphenopalatine ganglion This is established by the experimental finding that the vasoconstrictor effect of sympathetic stimulation in the cat is almost completely abolished by section of the vidian nerve or excision of the sphenopalatine ganglion (Figure 2)

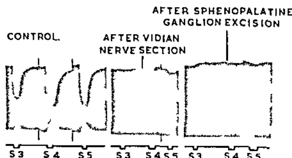


FIG 2 Typical record of effect of stimulation of cervical sympathetic on nasal resistance

Control shows vasoconstrictor effects produced by increasing strengths of stimulation This effect is abolished by section of vidian nerve and excision of sphenopalatine ganglion

This view is further supported by the experimental demonstration that the simultaneous stimulation of sympathetic preganglionic fibres and the vidian nerve produces no greater effect than maximal stimulation of the vidian nerve alone

(b) Stimulation of the Parasympathetic Innervation

The *vidian nerve* contains both parasympathetic preganglionic fibres and sympathetic postganglionic fibres This nerve and the sphenopalatine ganglion can be readily exposed for stimulation in the cat by a transorbital approach In later experiments we have found it more convenient to expose this nerve from the mouth by a transpalatal route This has the advantage of giving ready access to both preganglionic and postganglionic fibres

Stimulation of this nerve of the pterygoid canal (vidian nerve) produces two well defined types of response

The method used records graphically variations in the degree of congestion of the nasal mucosa by recording the pressure changes at the nostril when a fixed volume of air is pumped some fifteen to twenty times a minute along a cannula inserted into the nose of the tracheotomized animal

With a constant stroke volume maintained by the pump, the magnitude of the rise and fall of pressure is determined by the resistance in the nasal chamber Vasodilatation in the nose increases the obstruction and resistance in the nose and a greater excursion of the manometer results Vasoconstriction conversely will produce a diminished excursion on the record Thus changes in the resistance in the nasal airway are almost immediately reflected in the manometer record Connected by a side limb to the nasal cannula is a small atomizer, this permits intranasal insufflation of drugs By this method it is possible to record quantitatively changes in nasal resistance produced by changes in the nasal vascular bed

This technique has the merit of extreme simplicity and gives remarkably consistent results The graphic records give a quantitative measure of the intensity and the duration of changes in nasal resistance

(a) Stimulation of Cervical Sympathetic

The response to stimulation of the cervical sympathetic is an immediate and intense vasoconstriction The threshold of stimulation for this response is remarkably low mere handling of the sympathetic chain elicits a response This may be correlated with the clinical fact that warming over the superior cervical ganglion may clear the airway in an occluded and congested nose Increasing the strength of stimulation or the frequency of stimulation produces an increased degree of vasoconstriction However, beyond a certain maximum further increase in stimulation, as one would expect produces no further increase in response This maximal effect is a useful standard reference for contrasting the vasoconstrictor potency of various drugs The vasoconstrictor effect of stimulation of these preganglionic fibres is abolished by application of nicotine solution to the superior cervical ganglion

postganglionic sympathetic component of the vidian nerve passes through without interruption We have already considered experimental evidence that the postganglionic sympathetic fibres from the superior cervical ganglion pass along the vidian nerve

The vasoconstrictor component in the vidian nerve can be demonstrated to consist entirely of fibres from the superior cervical ganglion The sympathetic cervical ganglion was excised and the postganglionic fibres allowed to undergo degeneration Four weeks later, stimulation of the vidian nerve produced only marked vasodilator effects—at all strengths of stimulation (Figure 3) Thus superior cervical ganglionectomy is followed by loss of all the vasoconstrictor response produced by stimulation of the vidian nerve

Stimulation of the *great superficial petrosal nerve* and of the trunk of the *facial nerve* central to the geniculate ganglion produces as expected only vasodilatation

Some of the more important clinical implication of these experiments are that (1) section of the vidian nerve or excision of the sphenopalatine ganglion involves interruption of both the sympathetic and parasympathetic innervation of the nasal vessels and mucosal glands, and (2) parasympathetic denervation alone would require interruption of the greater superficial petrosal nerve or the facial trunk itself central to the geniculate ganglion

The recording of changes in resistance to air flow through the nose is perhaps not as convincing evidence of vascular changes as the direct visual observation of changes in colour and volume of the mucosa Sir Thomas Lewis s researches on the vascular responses of the skin serve as a classical example of the use of simple observations on skin colour, temperature and volume to resolve circulatory responses While the complexity of the turbinal area in the cat precludes direct observation through the external nares nevertheless by excision of the hard palate and so removing the floor of the nose we have been able to observe directly and to photograph changes in vascularity in swelling and in secretory activity [1]

[1] At this point in the original lecture a short section of a film showing the effect of stimulation of the sympathetic and parasympathetic nerve supply was shown.

(1) with weak stimulation there is produced vasodilatation and increased resistance This represents the effect of stimulation of parasympathetic fibres predominantly

(2) with stronger stimulation there results a vasoconstriction and reduction of nasal resistance, i e a dominance of the sympathetic effect (Figure 3)

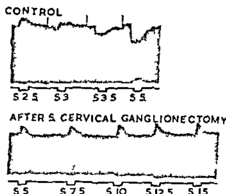


Fig 3 Biphasic effect of stimulation of vidian nerve on nasal vessels Upper record shows vasodilator effect of weak stimulation of nerve replaced by vasoconstriction with increased strength of stimulation Lower record shows that after degeneration following superior cervical ganglionectomy the response produced by vidian nerve stimulation at all intensities of stimulation is vasodilation

This diphasic response with varying strength of stimulation is correlated with the different diameters of the two types of nerve fibres known to be present The sympathetic postganglionic fibres are thin and non medullated and have a higher threshold of stimulation than the thicker medullated preganglionic parasympathetic fibres

The parasympathetic vasodilator effect with weak stimulation is potentiated by eserine and other anticholinesterases given intravenously or applied to the sphenopalatine ganglion Nicotine which blocks autonomic ganglionic synapses abolishes the parasympathetic effect when painted on the ganglion But the vasoconstrictor effect of strong stimulation persists

These experiments confirm that the parasympathetic preganglionic fibres relay in the sphenopalatine ganglion, while the

Reading has reported immediate and dramatic relief of profuse rhinorrhea by section of the preganglionic parasympathetic fibres in the great superficial petrosal nerve

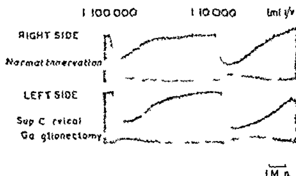


Fig 4 Simultaneous records of effects of intravenous adrenaline on normal and sympathectomized nasal vessels
Right side normal innervation *left side* (same animal) superior cervical ganglion excised four weeks previously

A most interesting case of geniculate herpes described by Monkhouse presented marked nasal vasoconstriction and dryness in the nose In one case of facial paralysis due to a lesion involving the first part of the facial nerve studied by Malcomson there was marked shrinkage of the nasal mucosa with drying and excessive crusting So severe was this effect that it constituted the main complaint of the patient

Sensitization

Sympathectomy has been known to result in hypersensitivity of the denervated blood vessels to minute amounts of circulating adrenaline This phenomenon can be well demonstrated in denervated nasal vessels of the cat (Figure 4) If similar hypersensitivity occurred and persisted in man one might be tempted to contemplate deliberately inviting post sympathectomy sensitization in the treatment of chronic nasal congestion rendering the nasal vessels hypersensitive and then maintaining nasal *vasoconstriction by very minute doses of sympathomimetic* drugs—doses below the threshold dose which would have significant effects on the heart and general circulation However

Clinical Studies in Man

I turn next to consider such evidence as is available from clinical studies of the effects on the human nasal mucosa of operations on the autonomic nervous system

(1) *Section of Sympathetic*

Fowler was the first to describe hyperaemia, hypersecretion and swelling of the nasal mucosa in patients following permanent interruption of the cervical sympathetic Later Wolf confirmed that temporary block of the sympathetic with procaine produces hypersecretion and vasodilatation We also have examined a small group of cases of Horner s syndrome following superior cervical ganglionectomy and verified these findings

The effects of sympathetic denervation in man have been closely studied by Gardner

(*a*) *Superior Cervical Ganglionectomy* This operation is followed by immediate and persistent nasal obstruction The mucous membrane is swollen, pale and secretion is increased Vasoconstrictor drugs produce rapid decongestion Biopsy showed no change in epithelium but some hyperplasia of mucous glands

(*b*) *Stellate Ganglionectomy* This is a preganglionic sympathectomy with respect to the nasal vessels Nasal obstruction is produced accompanied in about 50 per cent of cases by hypersecretion The mucous membrane here again shows swelling, pallor and a normal response to vasoconstrictor drugs

(*c*) *Anterior Rhizotomy* This operation produces the same effects in nasal mucosa as stellate ganglionectomy

(2) *Section of Parasympathetic Innervation*

Gardner and his associates resected the *great superficial petrosal nerve* in the treatment of unilateral headache—the object being to divide vasodilator fibres to the intracranial vessels It is of interest that this operation resulted in excessive dryness and crusting in the nose On examination the mucous membrane was shrunken as compared with the control side although the colour of the mucosa was unchanged Biopsy revealed a squamous metaplasia

Reading has reported immediate and dramatic relief of pro fuse rhinorrhea by section of the preganglionic parasympathetic fibres in the great superficial petrosal nerve

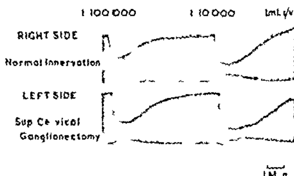


Fig 4 Simultaneous records of effects of intravenous adrenaline on normal and sympathectomized nasal vessels
Right side normal innervation *left side* (same animal) superior cervical ganglion excised four weeks previously

A most interesting case of geniculate herpes described by Monkhouse presented marked nasal vasoconstriction and dry ness in the nose In one case of facial paralysis due to a lesion involving the first part of the facial nerve studied by Malcom son there was marked shrinkage of the nasal mucosa with drying and excessive crusting So severe was this effect that it con stituted the main complaint of the patient

Sensitization

Sympathectomy has been known to result in hypersensitivity of the denervated blood vessels to minute amounts of circulating adrenaline This phenomenon can be well demonstrated in denervated nasal vessels of the cat (Figure 4) If similar hyper sensitivity occurred and persisted in man one might be tempted to contemplate deliberately inviting post sympathectomy sensi tization in the treatment of chronic nasal congestion rendering the nasal vessels hypersensitive and then maintaining nasal vasoconstriction by very minute doses of sympathomimetic drugs—doses below the threshold dose which would have signi ficant effects on the heart and general circulation However

Gardner failed to find any hypersensitivity of nasal vessels to adrenaline after ganglionectomy in man

DRUGS

Nose, nose, jolly red nose
And who gave thee this jolly red nose?
Nutmegs and ginger, cinnamon and cloves
And they *gave me this jolly red nose* [1]

A great and ever increasing variety of chemical substances is being applied daily to the human nasal mucosa, mainly with the object of producing vasoconstriction Several investigators, notably Sternberg, Jackson and Richtner, have studied the effect of drugs on the nasal mucosa of experimental animals *Sympathomimetic drugs*, applied locally, produce rapid vasoconstriction with blanching and shrinkage of the mucosa The nasal blood vessels are remarkably sensitive to minute quantities of circulating adrenaline Vasoconstrictor drugs used intranasally are in the main assayed for vasoconstrictor potency on peripheral blood vessels, and not on nasal vessels Here is surely a fruitful field, the investigation of the action of these drugs on human nasal vessels using the simple techniques of direct observation of mucosal colour, temperature and swelling

Parasympathomimetic drugs like mecholyl and neostigmine produce nasal congestion and increased secretion

The effect of histamine is of very special interest because of its relation to allergic rhinitis The classical researches of Dale on histamine have provided the physiological basis of our knowledge of nasal allergy The triple response of a red reaction, flare and wheal following the intradermal injection of histamine has been extensively analysed But extraordinarily enough there has been practically no direct experimental evidence of the effect of histamine on nasal blood vessels in man *The increased nasal resistance produced by intranasal insufflation* of histamine is readily demonstrated in the experimental animal (Figure 5) This method can be used to assay the relative potency of antihistamine drugs Undoubtedly the appropriate

[1] John Fletcher *The Knight of the Burning Pestle* I iii

test organ for assessing the efficiency of antihistaminic drugs for use in vasomotor rhinitis should be the nasal vascular bed

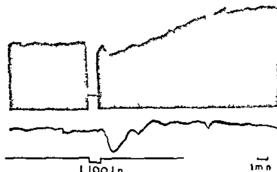


FIG 5 Vasodilator effect following intranasal insufflation of 1 per cent histamine

TEMPERATURE AND HUMIDITY OF INSPIRED AIR

When all aloud the wind doth blow
  And coughing drowns the parson s saw
And birds sit brooding in the snow
  And *Marion s nose looks red and raw*
When roasted crabs hiss in the bowl [1]

The nasal blood vessels respond rapidly to changes in temperature of inspired air, and the mucosal blood flow is in this way automatically adjusted to changes in climatic conditions A reduction in atmospheric air temperature is compensated for by arteriolar dilatation with a consequent increased blood flow This greater blood flow raises and maintains the mucosal temperature and the mucosa thereby acts as a more efficient heat radiator In this way adequate heating of the colder inspired air up to body temperature is ensured

Shakespeare appreciated the heating potential of the nose for he has Falstaff speak of Making his nose do office as a warming pan for his sheets And earlier Falstaff says of Bardolph s nose Thou art an everlasting bonfire thou has saved me a thousand marks in links and torches, walking with me in the night twixt tavern and tavern

[1] W Shakespeare *Love s Labour s Lost* V ii 920–4

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cutaneous cooling [illegible] in a warm subject produces initial vasoconstriction followed by hyperaemia. This is well shown from the experiments of [illegible] and Holmes. Local cooling was carried out by applying [illegible] towels together with a blast of cold air to the shoulders. The reflex response is pallor and swelling of turbinates followed by marked hyperaemia. Associated with these vascular changes is an increase in secretion, late in onset and persisting after cessation of cooling. These observations would appear to substantiate to some extent the popular belief in the relationship between sitting in a cold draught and nasal congestion. In the words of Leonard Hill (19[illegible]): "In those conditions which are unfortunately only too common—where the feet are chilled by a draught along a cold floor—while the head is immersed in warm stagnant air—the nasal mucosa is swollen, congested and covered with secretions." Hill accounted in this way for the feeling of stuffiness and headache in crowded and overheated places of assembly. These were the conditions in the House of Commons of his day where in his words "air introduced through the floor cools the feet of the hot-headed members of that House".

EMOTIONAL STRESS

It has long been recognized that emotional states affect the degree of congestion of the nasal mucous membrane. But it is only in recent years that the vasomotor and secretory responses of the mucous membrane of the human nose to emotional stress and hazardous life situations have been the subject of detailed and precise experimental investigation by Holmes and his colleagues. These workers applied to the study of the nasal mucosa the techniques so successfully used for following by direct observation the changes both qualitative and quantitative in the human gastric mucosa in response to emotional stimuli.

In the human nose two main patterns of response were identified.

(1) fear and terror: there was [illegible] [illegible] and shrinkage of the nasal [illegible] [illegible] type of response, opening up the [illegible]

(2) emotional conflicts [illegible]

22

This aspect of nasal circulatory physiology is of especial interest in relation to the problems of comfort and the ventilating and heating of crowded buildings

The consistent effects produced by changes in air temperature are well illustrated in the experiments of Trueting After a control period in a comfortably warm room, the warmly clad subject is transferred to a cold room (45° F) The first effect is a moderate hyperaemia with redness, swelling and increased secretions Later the redness subsides but the swelling persists

Effect of Cutaneous Heating and Cooling

In the experiment just considered the subject is kept warm while the inspired air is cooled Another interesting problem is that of the effects on nasal vessels of warming or cooling the whole body surface

General cutaneous warming causes swelling and hyperaemia When the temperature change is rapid, such as walking into a hot room, the nasal hyperaemia is marked A gradual slow rise of temperature has a much less obvious effect

In the years 1931–3 Leonard Hill published a series of papers on the relation between heating of the body and the width of the nasal airway He proved that the effective rays were in the infra red part of the spectrum Rays in the range 25,000–30,000 Å produced nasal congestions Rays of wavelengths outside this range produced opening up of the nasal passages Van Dishoeck has confirmed that longer wavelengths in the infra red constantly cause nasal congestion Thus an illuminating source of heat like the tungsten lamp opens up the nasal airway, and the electric fire tends to cause nasal obstruction

General cutaneous cooling In a series of experiments between 1919 and 1921 Mudd and his associates demonstrated a fall in nasal mucosal temperature as a reaction to general cutaneous cooling Spiesman and later Ralston and Kerr reinvestigated this problem While they confirmed that the initial response to exposure to general cooling was a fall of nasal temperature and shrinkage of mucosa, they discovered that the mucosa later swells although the mucosal temperature is still falling

Local cutaneous cooling By contrast with the effects of general

cutaneous cooling local cooling of part of the body in a warm subject produces initial vasoconstriction followed by hyper aemia This is well shown from the experiments by Trueting and Holmes Local cooling was carried out by applying ice cold towels together with a blast of cold air to the shoulders The reflex response is pallor and swelling of turbinate followed by marked hyperaemia Associated with these vascular changes is an increase in secretion, late in onset and persisting after cessation of cooling These observations would appear to substantiate to some extent the popular belief in the relationship between sitting in a cold draught and nasal congestion In the words of Leonard Hill (1924) In those conditions which are unfortunately only too common—where the feet are chilled by a draught along a cold floor—while the head is immersed in warm stagnant air—the nasal mucosa is swollen congested and covered with secretions Hill accounted in this way for the feeling of stuffiness and headache in crowded and overheated places of assembly These were the conditions in the House of Commons of his day where in his words air introduced through the floor cools the feet of the hot headed members of that House'

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In the human nose two main patterns of response were identified

(1) fear and terror these produced vasoconstriction and shrinkage of the nasal mucosa This is a sympathetic type of response, opening up the nasal airway,

(2) emotional situations causing frustration and resentment

or humiliation produce a very different response, which is characterized by marked vascular engorgement, with obstruction of the nasal passages and by an increased volume of secretions. Here we have a response resembling the effects of parasympathetic stimulation.

A most convincing demonstration of the hyperaemia, lymphatic engorgement and hypersecretion in emotional states of frustration and rage was provided by comparing the histological sections of a biopsy of the inferior turbinate of a subject during a period of intense emotional conflict with sections of a similar biopsy from the same subject during a control period of relaxation and security.

They believed that these histopathological changes might become irreversible. Thus the recurrent emotional conflicts which begin by giving you attacks of nasal congestion may qualify you to become a chronic sufferer from nasal disease.

Other Reflex Effects

The nasal vessels may also be involved in some of the generalized sympathetic vasomotor responses in the body. Painful stimulation of peripheral cutaneous areas results in nasal vasoconstriction. When Tschallusow investigated the reflex effects of stimulation of central end of the sciatic nerve and other peripheral afferent nerves, he concluded that the nasal mucosa was the most sensitive index available of changes in peripheral vasomotor tone. The delightful Edward Lear in his nonsense songs would appear to have grasped this point when he says 'No harm can come to his toes if his nose is warm.'

Asphyxia is associated with nasal vasoconstriction (Tatum). This effect is prevented by section of the cervical sympathetic and is therefore reflex in origin. Overventilation, on the other hand produces dilatation of nasal vessels. This response is not affected by sympathectomy. These effects would appear to subserve a useful function: an adaptive reflex mechanism, reducing nasal resistance when the respiratory need is increased, and increasing resistance when respiration is depressed.

Blocking of venous outflow of the head produces, as one would anticipate, nasal congestion. This may account for

When the coma does not cease promptly after the administration of glucose and oxygen *vasodilators* such as amyl nitrite inhalation or intravenous injection of nicotinic acid may be successful[115 116] Injections of *calcium* gluconate or potassium salts are indicated[16 6] in cases associated with hypocalcemia or hypopotassemia Convulsions respond to this treatment or to barbiturates

As long as the patient is *able to swallow* he is given five to ten lumps of sugar or 6 to 8 tsp sugar in a glass of water sweetened fruit juice ginger ale or milk This is repeated at short intervals until the major symptoms disappear but not longer Overdose of sugar may overcome the hypoglycemia for one to four hours then induce a secondary hypoglycemia

Minor attacks are treated by oral administration of sugar or starch such as crackers Melba toast etc The starches do not act so rapidly but are less likely to cause overstimulation of the islets and secondary hypoglycemia Some patients prefer a raw or soft boiled egg milk candy or sweet liquor Many patients carry some carbohydrate in their pockets

The Interval between Attacks and the Chronic Hyperinsulinism —The principle of management is the prevention of hypoglycemia precipitating factors as well as sedation of the beta cells including their regulatory apparatus and if necessary treatment of chronic hypoglycemia

Rules of Living in the Interval —The patient should *avoid* (1) long intervals between meals irregular and delayed meals skipping meals and big meals at parties (2) pure sugar candy chocolate sweets (3) fats in large quantity (4) very cold food and drinks ice cream (a triple offender) coffee chocolate and soft drinks especially the cola drinks (5) undue muscular exercise any overwork or tiring occupation prolonged shopping etc (6) emotional upsets crowds and overheated rooms

Diet in the Interval —Individual quantitative and qualitative regulations of the diet are required The following *principles* of diet should be followed

1 Caloric intake is adjusted to the individual needs depending on whether there is obesity or emaciation The pathologic hunger often causes a tendency to overfeeding One patient was able to prevent his attacks by staggering his food intake When first seen he was taking 5 000 calories daily with a weight increase from 150 to 250 lb Nevertheless it became increasingly difficult to prevent attacks[8] Overfeeding causes increased hyperemia of the pancreas and increased intestinal reflexes to the pancreatic vagus system Both factors stimulate the islets A vicious circle has set in In patients who are overweight the caloric intake should be reduced and benzedrine drugs given as much as hunger and tendency to attacks permit In those underweight 35 to 40 calories per kilogram of body weight are recommended[90]

2 Frequent feedings of the above caloric intake *e g* six meals a day three of them larger meals of equal quantity and in between three small meals with half the quantity If necessary also feeding during the night

3 Selection of foods which exert the least possible stimulation of the internal as well as the external secretion and which are adequate to the individual efficiency of the external secretion

Protein in isoglucogenic quantities is the least stimulating for hyperirritable beta cells and the least hypoglycemic of all food [94] Intolerance to meat especially fatty meat or to excess of protein must be compensated for by pancreatin (see p 524)

Fat and its split products also cause only mild and delayed direct stimulation of the insulin secretion However fat is a most powerful stimulant for the exocrine apparatus inducing hyperemia and increased vagus tone in the pancreas These in turn may extend upon the internal secretion When the hyperinsulinism is associated with exocrine disease fats may elicit the triad of pain indigestion and hypoglycemia Pancreatin makes possible the administration of sufficient amounts of fat

Starch is converted to sugar and absorbed as such more rapidly than protein and fat but slower than sugar It stimulates the beta cells less acutely and is less likely to cause secondary hypoglycemia than is sugar Prolonged and marked overloading with starch increases the irritability of the beta cells Many patients do well with low starch diet however some require substantial amounts of starch in order to control their hypoglycemia [19 92]

Sugar is effective in abolishing hypoglycemia quickly yet it has the greatest tendency to elicit secondary hypoglycemia and to increase the hyperirritability of the beta cells Sugar is indicated in the attack contraindicated in the interval

Diets —Various formulas are employed all with low carbohydrate elimination of free sugar and frequent feeding

1 High protein diet of Conn [70 93 94]
2 Standard diabetic diet with addition of protein according to Wilder [8]
3 High fat diet of Harris and others [8 74 95–97]
4 High vegetable diet of Hagedorn [9]

The high protein diet is especially recommended in mild neurogenic hypoglycemia There it may reduce the ravenous appetite as well as the frequency and severity of attacks A high fat diet must not be forced upon the patient when signs of intolerance to fat appear such as aversion to fat dyspepsia pancreatic pain or increased hypoglycemia The high vegetable diet of Hagedorn tends to combat the hunger with food which is voluminous but does not induce hypoglycemia

The author uses the following diet (1) High protein (140 gm) with liberal amounts of milk cheese lean meat (2) Medium fat (100 gm) with adequate butter cream and vegetable fat (3) Medium starch (150 gm) No sugar Sufficient pancreatin is added for reasons discussed in the next paragraph

Medication in the Interval In addition to regulation of the diet the following four medications are very useful They act by inhibition of the nervous and other stimulation of the islet

1 *Pancreatin* —Pancreatic enzymes can be valuable in the management of hyperinsulinism In the first place they aid in the utilization of fat and meat as mentioned above They are especially important in the high protein and high fat diets In the second place a surplus of extrinsic pancreatic enzymes may reduce the activity of the acinar system and therewith the hyperemia of the pancreas and associated overactivity of the beta cells

Prolonged administration of pancreatin in nonneoplastic cases of hyperinsulinism was successful in converting the hypoglycemic blood sugar tests to normal tests [31, 59]

2 *Atropine and Its Equivalents* — They reduce the physiologic and the pathologic stimuli of vagal innervation of the islets. By this they elevate in neurogenic hyperinsulinism the flat blood sugar tolerance curve to normal level [8, 13, 4]

3 *Barbiturates* —They prove to be beneficial not only in neurogenic cases where they reduce the origin of the pathologically increased nervous stimuli of normal beta cells but also in some cases of adenoma where they reduce the nervous stimulation of adenoma cells [8, 99]. In a case of coma with severe extensor spasms intravenous administration of sodium amytal was successful [8]

4 *Estrogenic Hormones* – In menopausal and amenorrheic hyperinsulinism estrogenic hormones offer considerable relief presumably by suppression of pituitary overactivity

Three other medications suggested on the basis of theoretical considerations have not proved of value thus far. Thyroid medication up to a basal metabolic rate of plus 30 per cent may prevent attacks[8] but may be harmful to the heart and other tissues (See also p 502.) The use of alloxan has not yet been justified on the basis of clinical reports [1, 119] and neither has the use of diabetogenic anterior pituitary substance. Both substances (see p 506) are stimulants of the beta cells and cause diabetes by exhaustion and the cure of the hyperinsulinism would have to be paid for by provocation of permanent diabetes. This is justified in cases of inoperable adenoma or carcinoma. ACTH in dosage of 18–20 mg every two days administered for 5 months relieved a patient from hypoglycemic symptoms for the duration of the treatment [10]

Surgical Management of Hyperinsulinisms —The indications for surgery have been defined on page 550. As soon as the diagnosis of surgical hyperinsulinism is made operation is advisable. Delay increases the operative risk which is greater after cerebral damage or marked obesity has developed

The contributions of surgery are (1) clarification of the diagnosis (2) elimination of the cause of hypoglycemia and (3) prevention of future brain damage and malignant degeneration

The surgical procedures are

1 Painstaking *exploration* (inspection and palpation) of the anterior as well as the posterior part of the pancreas which requires mobilization of the posterior wall. The existence of multiple microscopic or ectopic adenomas must be kept in mind. Adenomas have eluded the most expert surgeons e g 78 times in 400 cases during the first operation [1]

2 *Enucleation* is the operation utilized in distinct adenoma without metastases. Excision of ectopic adenomas is indicated. These procedures were done in 152 of 200 operations reviewed by Howard *et al* [1]

3 *Pancreatectomy* is indicated when malignancy is present when multiple adenomas cannot be enucleated and when the operative finding is negative and the hypoglycemia dangerously severe. The latter procedure is called blind resection. The purpose of resection of an apparently nonneoplastic pancreas is to remove overlooked adenomas or hyper

functioning nonadenomatous islet tis ue The re ults of blind re ection are called striking by some authors disappointing by others Lack of improvement has been attributed to incomplete resection l ancre atectomy of course increases the operative ri k Pancreatectomy was done in 48 of the 200 operations reviewed by Howard *et al* The pancreatectomy is either (1) distal in adenoma of the tail that cannot be enucleated easily (2) subtot il in the absence of palpable adenom i (3) tot il as a secondary procedure after failure of (2)[119] For preoperative and postoperative management see reference 119

4 *A second and third operation* have proved to be justified in several cases which were negative at the first operation when the patient continued to suffer from severe hypoglycemia

TABLE 44 —RE ULTS OF 200 CA E OPERATED I ION FOR I LET CELL ADENOMA (152 ENUCLEATION 48 SUBTOTAL RE ECTION)

	P r ntag
1 Permanent reli f from hypoglycem ia	) 5
2 *Tran itory relief from hypogly em ia*	2 0
3 No relief from hypoglycemia	9
4 Death from operation	) 0
5 R ult unreported	0

Results of Surgery —The over all results of surgery are very satisfactory (see Table 44) especially in view of the fact that nonoperative cases with severe adenomatous hyperinsulinism die from hypoglycemia within six months to three years[1] *Total removal of a functioning adenoma offers total cure* as shown by follow up periods of five to thirteen years The hypo glycemia disappears immediately after the removal of the adenoma

In enucleation lies the risk that an overlooked second adenoma may cause recurrence after an initial period of improvement The operative risks of resection are an 8 to 10 per cent operative mortality and complica tions such as intra abdominal accumulation of pancreatic fluid pseudo cysts and pancreatic fistula in addition to the general complications of abdominal surgery One half of 1 per cent of the patients died of fatal hyperthermia of unknown origin After subtotal re ection the majority of the patients became diabetic for three to five days only 2 per cent of the 200 cases became diabetic permanently Irreversible brain lesion are of course not influenced by the operation

BIBLIOGRAPHY

1 HOWARD J M MOS N H and RH D J E Hyp ulinism r I I let Cell Tum o of I i a w th 398 R rt I Tum r Surg C ve & Ol t 90 417 1 ɔ0
2 CIBSON R B and L RIMER R M Hyp gly mi S mptom I ovoked by Re peated Gluco Inge ti n C f R ual Dist t J A M A 8 408 1924
3 HARRI S Hyper ul n i ı Dy ulı J A M A 83 29 1924
4 ——— H i ul I Dy m ulı m (In ul g ne Hy gly emia) Endo rıcl gy 16 1 33
5 WILDER R M ALL N F N I FR M H I R BERT ON H I Carcinoma of the I lan ls of th I H i ulın ı and H gl e ia J A M A 89 348 1 r

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37 Banting F G and Best C H Internal Secretion of the Pancreas J Lab & Clin Med ~ 251 1922
8 Mansfeld G Surgical Treatment of Diabetes Klin Wchnschr 3 2378 1924
39 Herxheimer G Islets of the Pancreas and Insulin after Ligation of the Pancreatic Ducts Klin Wchnschr 5 2299 1926
40 Mansfeld G Attempts of Surgical Treatment of Diabetes Klin Wchnschr 7 14 1928
41 Friedlaender E On the Relations between Internal and External Secretion of the Pancreas The Problem of Herxheimer Mansfeld Phenomenon in Pancreolithiasis Ztschr f klin Med 1 8 63 1935
42 Mansfeld G On the Relations between Internal and External Secretion of the Pancreas Rectification to the Publication of Friedlaender Ztschr f klin Med 1 8 63 1935
43 Brinck J and Sponholz G Hypoglycemia in Pancreolithiasis Deutsche Ztschr f Verdauungs u Stoffwechselkrankh 1 3 1938
44 Ehrstroem R and Nylander G Chronic Pancreatitis as Complication of Diseases of Biliary Passages and of Gastric Ulcer Finska lak sallsk handl 3 513 1931
45 Ehrstroem R Chronic Pancreatitis with Hyperinsulinism (Glycopenia) Acta med Scandinav 77 334 1932
46 Fabrykant M and Berger M Dynamics of the Hypoglycemic Reaction Am J M Sc 216 84 1948
47 Bergmann G von and Katsch G Pathologic Physiology of Special Clinical Feature Handbuch d normalen und pathologischen Physiologie ed by A Bethe G V Bergman G Embden A Ellinger Berlin Springer Vol III B 2 p 1159 192
48 Bergmann G von Funktionelle Pathologie Berlin Springer 1936
49 Pllech A and Rimbaud P The Glucose Regulation Function of the Pancreatic Islets General Physiopathology of Pancreatic Diabetes Montpellier med 1 1 1935
50 Berger W A and Schnetz H The Function of the Pancreas in Biliary Tract Diseases Deutsches Arch f klin Med 18 1 1939
51 Katsch G and Brinck J The Diseases of the Pancreas in Handbuch d inneren Medizin edited by G Bergman and R Staehelin 3rd ed Berlin Springer 1938
52 Hecge I Diastase and Blood Sugar Examination in Diagnosis of Pancreatic Nork Klin Lagevi len k 91 182 1930
53 Beckmann T M Contributions to the Diagnosis of the Surgical Pancreopathies Acta chir Scandinav 8 Suppl 1 193
54 Carlson A J and Ginsberg H The Influence of Pregnancy on the Hyperglycemia of Pancreatic Diabetes Am J Physiol 36 21 1915
55 Cutbert F P Ivy A C Isaacs B L and Gray J The Relation of Pregnancy and Lactation to Extirpation Diabetes in the Dog Am J Physiol 11 480 1936
56 Gordon W H Fetal Hypoglycemia Due to Hyperinsulinism J Michigan M Soc 13 167 1935
57 Dubreuil G and Anderodias J Giant Islets of Langerhans in the Newborn Child of a Diabetic Mother Compt rend Soc de biol 83 1490 1920
58 Gray S H and Feemster L C Compensatory Hypertrophy and Hyperplasia of the Islets of Langerhans in the Pancreas of a Child Born of a Diabetic Mother Arch Path and Lab Med 1 348 1926
59 Phillips A W Hypoglycemia Associated with Hypertrophy of the Islands of Langerhans J A M A 96 1195 1931
60 Ehrich W On Congenital Hypoglycemia Klin Wchnschr 13 84 1934
61 Gordon W H Compensatory Hypertrophy and Hyperplasia of Islands of Langerhans Etc so Congenital Hypoglycemia Due to Hyperinsulinism Ohio State M J 3 540 1936
62 Okkels H and Brandstrup E Th [illegible] Hypophysis and [illegible] in Children of Diabetic Mothers Acta path et microbiol Scandinav [illegible] 1938
63 H [illegible] B Hypertrophy and Hyperplasia of Islets of Langerhans in Infants of Diabetic Mothers Arch Int Med [illegible] 1940

6 MALAMUD N and GROSH L C JR Hyperinsulinism and Cerebral Changes Arch Int Med *61* 5(9 1938
7 DAVID V C Pancreatectomy for Hypoglycemia Surgery *8* 212 1940
8 WILDER R M *Clinical Diabetes Mellitus and Hyperinsulinism* Philadelphia Saunders 1940
9 CLARK C A The Influence of the Vagus on the Islets of Langerhans I Vagus Hypoglycemia J Physiol *59* 446 1925
10 LABARRE J On the Increase of Insulin in the Venous Blood of the Pancreas following Vagus Stimulation Compt rend Soc de biol *96* 193 1927
11 DIETRICH S Studies on Diabetes and Insulin XII The Direct Evidence of the Insulin Secretion of the Pancrea Arch f exper Path u Pharmakol *1 5* 336 1927
12 CELLHORN E *Autonomic Regulations* New York Interscience 1943
13 PORTIS S A Life Situations Emotions and Hyperinsulinism J A M A *14?* 1281 1950
14 ——— The Medical Treatment of Psychosomatic Disturbance J A M A *1 6* 413 1944
15 SCHNETZ H Changes of the External Secretion of the Pancreas in Artificial Fever Ztschr f d ges exper Med *11 /* 208 1943
16 ALEXANDER F and PORTIS S A A Psychomatic Study of Fatigue in Neuropsychiatric Patients Psychosom Med *6* 191 1944
17 JOSLIN E P ROOT H F WHITE P and MARBLE A *The Treatment of Diabetes Mellitus* 9th ed Philadelphia Lea & Febiger 1952
18a HABERER H VON Diagnostic and Therapeutic Errors in Digestive Diseases and Their Prevention Verhandl d Gesellsch f Verdauung kr *8* 252 1929
18b ——— Influence of Affections of the Pancreas upon the Indication to Early Surgery of Biliary Tract Diseases Med Klin *5* 1571 1929
19 LAPP R W and DIBOLD H Gastric Secretion and Hypoglycemia Klin Wchnschr *10* 1221 1931
20 ——— The Activity of the Stomach in Relation to the Blood Sugar Level Deutsches Arch f klin Med *17* 550 1932
21 DIBOLD H Nutritional Disturbances following Resection of the Stomach Med Klin *2 ?* 1138 1933
22 BECKERMANN F Spontaneous Hypoglycemia following Resection of the Stomach Deutsche med Wchnschr *? 1* 683 1933
23 KORANJI A Spontaneous Hypoglycemia following Resection of the Stomach Deutsche Arch f klin Med *1 8* 353 1936
24 STRAATEN T and HUENERMAN M The Hypoglycemia of Patients with Gastric Disease in Its Significance for Gastric Surgery Med Klin *3 /1* 502 1936
25 KONJETZNY C F *The Inflammatory Basis of the Typical Ulcers of Stomach and Duodenum* Berlin Springer 1930
26 ——— Gastroduodenitis Med Klin *32 1* 473 1936
27 KAPP H Clinical Feature of Some Digestive Disease Schweiz med Wchnschr *6* 52? 1937
28 SCHNETZ H Duodenitis Deutsche Arch f klin Med *18* 570 19 8
29 ADLER BERG D and HAMMERSCHLAG E The Postgastrectomy Syndrome Surgery *1* 790 194 —Mechanism of the Postgastrectomy Syndrome J A M A *1 /* 429 1949
30 BERGER W Hyperinsulinism in Duodenal Ulcer Hyperinsulinism in Pluriglandular Disease Wien klin Wchnschr 253 1934
31 BERGER W Hyperfunctions of the Pancreas Klin Wchnschr *1* 1385 1938
32 SCHNETZ H Functional Test of the Islets of Langerhans in Hyperinsulinism Deutsche Arch f klin Med *1 9* 406 1936
33 BERGER W and SCHNETZ H Autoptic and Bioptic Controls of Pancreatic Function Tests Deutsches Arch f klin Med *184* 1 1939
34 HOFFMAN J *Female Endocrinology* Philadelphia Saunders 1944
35 WEIL A Quoted by HARRIS S Endocrinology *16* 29 1932
36 SOBOLEW L Structure of the Pancreas Zentralbl f allg Path u path Anat *11* 202 1900

93 CONN J W High Protein Diet in Treatment of Spontaneous Hypoglycemia J Clin Investigation 15 673 1936
94 CONN J W and NEWBURGH L H The Glycemic Response to Isoglucogenic Quantities of Protein and Carbohydrate J Clin Investigation 15 665 1936
95 WATER W C JR Spontaneous Hypoglycemia The Role of Diet in Etiology and Treatment South M J 24 247 1931
96 SHEPARDSON H C Glycopenia The Efficacy of High Fat Diets in the Treatment of Chronic Hypoglycemia Endocrinology 16 182 192
97 CLARK B B and GREENE J A Effect of Low Carbohydrate Diet on Glucose Tolerance in Spontaneous Hypoglycemia Proc Soc Exper Biol & Med 3 1459 1935
98 HAGEDORN H C Spontaneous Hypoglycemia Acta med Scandinav 80 18 1932
99 KELLER E J and WALTERS W Chronic Hypoglycemia Caused by Hyperinsulinism Cure Effected by Removal of an Adenoma of the Pancreas Proc Staff Meet Mayo Clin 4 4 1 1J C
100 FELLER I SALTZ S and HAUN I Syndrome of Adenoma of the Pancreas Bull Neurol Inst New York 4 310 1935
101 MAXEINER S R and BENDY H E Islet Cell Tumor of the Pancreas Surgery 18 1 1 1[illegible]
102 GOOD T I Origin and Growth of an Adenoma of the Islands of Langerhans Surgery 18 1[illegible] 194[illegible]
103 SOBOLEW L W Struma of the Langerhans Islets of the Pancreas Virchows Arch f path Anat 17 123 1904
104 PROOBOROWSKY N Adenoma of the Pancreas Frankfurt Ztschr f Path 13 390 1913
105 TERBRUEGGEN A Anatomical Findings in Spontaneous Hypoglycemia Due to Multiple Islet Cell Adenoma Beitr z path Anat u z allg Path 88 3 1931
106 CECIL R L Concerning Adenomata Originating from the Islands of Langerhans J Exper Med 13 [illegible] 1911
107 PRIESEL A Contribution to the Pathology of the Pancreas in Particular the Adenoma and the Autonomy of the Islets of Langerhans Frankfurt Ztschr f Path 6 453 1921
108 ROLLETT H Pure Adenoma of the Pancreas Frankfurt Ztschr f Path 10 268 1912
109 HICKEL P and NORDMANN J Solid Endocrine Adenomas of the Pancreas Bull et mém Soc anat Paris 33 18 1923
110 SMITH M C and SEIBERT M C Tumors of Islands of Langerhans and Hypoglycemia Am J Path 2[illegible] 1931
111 O'LEARY J L and WOMACK N A Histology of Adenoma of Islets of Langerhans Arch Path [illegible] 1934
112 WHIPPLE A O and FRANTZ V K Adenoma of Islet Cells of Pancreas with Hyperinsulinism A Review Ann Surg 101 1299 1935
113 [illegible] Tumors of Pancreas Am J Path [illegible] 1938
114 JONES C M [illegible] Case Reports Am J Med S[illegible]
115 RUTH[illegible] and RICHARD B W Observations on [illegible] J Nerv & Ment Dis 10 421 1945
116 SINCLE[illegible] J A [illegible] Factor in Hypoglycemia J Nerv & Ment D 10 [illegible]
117 [illegible] WINKLER A W T[illegible] F H L and PETER[illegible] The Intra[illegible] J Clin Investigation [illegible]
118 [illegible] C W [illegible] M J [illegible] 42 [illegible]
119 C[illegible] R B and WARREN K W Surgery of the [illegible] W B Saunders [illegible]
120 M[illegible] BECKER [illegible] ZIEGLER M R and WRIGHT W S The Metabol[illegible] Effect of [illegible] Spontaneous Hypoglycemia [illegible] ACTH [illegible] The Bl[illegible] [illegible]

64 MILLER H C and WILSON H M Macrosomia Cardiac Hypertrophy Erythroblastosis and Hyperplasia of Islands of Langerhans in Infant Born to Diabetic Mother J Pediat 23 251 1943

65a FABRYKANT M and PACELLA B L Associated Spontaneous Hypoglycemia with Hypocalcemia and Electrocerebral Dysfunction Arch Int Med 81 184 1948

65b ——— Labile Diabetes Electroencephalographic Status and Effect of Anticonvulsive Therapy Ann Int Med 9 860 1948

66 LLOYD P C Hypophyseal Tumor with Associated Tumor like Enlargement of Parathyroids and Islands of Langerhans Bull Johns Hopkins Hosp 45 1 1929

67 KALBFLEISCH H Adenomas of the Endocrine Glands in Hypoglycemia Frankfurt Ztschr Path 50 462 1937

68 FRANTZ V K Tumors of Islet Cells with Hyperinsulinism Benign Malignant and Questionable Ann Surg 11 161 1940

69 LANG F J Tumors of the Pancreas Arch f Path Anat 257 235 1925

70 CONN J W and CONN L Metabolism in Organic Hyperinsulinism Arch Int Med 68 876 1105 1941

71 WILDER J Anterior Pituitary and Pancreas Am J Digest Dis 15 183 1948

72 BRUNSCHWIG A The Surgery of Pancreatic Tumors St Louis Mosby 1942

73 CRAHAM E and WOMACK N The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and Other Conditions Surg Gynec & Obst 56 728 1933

74 HARRIS S Hyperinsulinism J A M A 101 1958 1933

75 BENSLEY R Structure and Relationship of the Islets of Langerhans in Harvey Lecture Series X Philadelphia Lippincott 1944–1945

76 MOERSCH H and KERNOHAN J Hypoglycemia Neurologic and Neuropathologic Studies Arch Neurol & Psychiat 39 242 1938

77 RYNEARSON F Adenoma of the Islets of Langerhans Proc Staff Meet Mayo Clin 11 451 1936

78 HIMWICH H E BOWMAN K M WORTIS J and FAZEKAS J F Biochemical Changes Occurring in the Cerebral Blood during Insulin Treatment of Schizophrenia J Nerv & Ment Dis 89 273 1939

79 ——— Changes in the Cerebral Blood Flow and Arterio-venous Oxygen Difference during Insulin Hypoglycemia J Nerv & Ment Dis 93 362 1941

80 SECKEL H P C Postmortem Hepatic Glycogenolysis in Hyperinsulinism and Glycogen Disease J Clin Investigation 18 723 1939

81 BAUMANN L and WHIPPLE A O Pancreatic Function Tests Am J M Sc 207 281 1944

82 HIMWICH H E Cerebral Metabolism and Electrical Activity during Insulin Hypoglycemia in Man Am J Physiol 120 559 1937

83 HIMWICH H E FROSTIG J P FAZEKAS J F and HADIDIAN Z Mechanism of Symptoms of Insulin Hypoglycemia Am J Psychiat 96 371 1939

84 HOAGLAND H CAMERON D E and RUBIN M A The Electroencephalogram of Schizophrenics during Insulin Treatment Hypoglycemia and Recovery Delta Index a Clinical Measure Am J Psychiat 94 183 1937

85 GOODWIN J W Bio-electrical Response in Metrazol and Insulin Shock Am J Psychiat 96 1389 1940

86 FERRARO A and JERVIS G A Pathologic Considerations on Insulin Treatment of Schizophrenia Am J Psychol 96 103 1939

87 BALLINGER J Hypoglycemia from Metastasizing Insular Carcinoma of Aberrant Pancreatic Tissue in the Liver Arch Path 32 277 1941

88 BICKEL G MOZER J J and JUNET R Diabetes with Severe Malnutrition Disappearance of Glycosuria and Progressive Diminution of an Islet Cell Carcinoma with Massive Metastases in the Liver Bull et mém Soc méd de Hop de Paris 61 12 1945

89 SCHNETZ H Serial Examinations and Therapeutic Alteration of Pancreatic Function in Two Cases with Typical Cholangiogenous Pancreopathy Ztschr f klin Med 131 501 1936

90 BOAS H I Gastroenterology Philadelphia Saunders Vol 3 1946

91 LOWREY L Diet in Etiology and Treatment of Mental Disorders Resulting from Hyperinsulinism Tri State M J 5 1012 1930

92 WILDER J Malnutrition and Mental Deficiency Nerv Child 3 174 1944

B Large cysts (potentially large)

4 Proliferation cyst (epithelial lining) benign cystadenoma and congenital solitary cyst (about 50 cases on record)[8]

5 Dermoid cyst

6 Parasitic cyst echinococcus *Cysticercus cellulosæ* (about 104 cases on record)[9]

7 Pseudocyst (no epithelial lining)

Symptomatology—The bulk of the benign enlargements of the pancreas in particular the solid neoplasms and small cysts are asymptomatic and are just incidental findings at operation

Diagnosis is possible only with adequate size and proper site of the tumor It can be based upon a triad of signs (*a*) epigastric mass (*b*) signs of a chronic pancreopathy and (*c*) benign disease The manifestations may go back for years or for only a few weeks

a Epigastric Mass—There are direct and/or indirect clinical and roentgenologic symptoms of a mass located in the mid-epigastrium or to the right or left side The direct *clinical* symptom is a visible and/or palpable tumor which is firm smooth painless or tender often presenting transmitted aortic pulsation and respiratory motility (See also cysts p 562) The indirect clinical symptoms are due to displacement compression or obstruction of adjacent organs They may be

1 Dyspnea and heart symptoms owing to elevation of the diaphragm in case of a very large tumor

2 Fullness of the stomach feeling of a small stomach nausea vomiting up to hyperemesis

3 Gaseous distention constipation partial mechanical ileus owing to gradual intestinal obstruction The digestive symptoms such as nausea vomiting gas syndrome and constipation are not always of mechanical origin Some may be caused also by pancreatico intestinal reflexes or pancreatic deficiency

4 Posthepatic icterus

5 Upper gastro intestinal hemorrhage (manifest or occult) owing to compression congestion and rupture of gastro-intestinal veins ascites

6 Hydronephrosis (rare)

The *roentgenologic* findings (p 448) as a rule are earlier and more definite than the clinical symptom

b Signs of a Chronic Pancreopathy Especially Pancreatic Dysfunction—The tumor may partially or completely obstruct the pancreatic duct and bring about atrophy of wide areas of the pancreas by long lasting obstruction and or by direct pressure upon glandular tissue The symptoms may be

1 Pain of pancreatic type (p 417) associated with hyperenzymemia either constant or recurrent attacks over years The pain however is often absent

2 Anorexia Nausea

3 Fat and meat intolerance Gaseous indigestion Recurrent or persistent diarrhea Steatorrhea Creatorrhea

4 Deficient external secretion in duodenal content test Dilatation and secondary infection of the duct system

Chapter 27

THE BENIGN TUMORS OF THE PANCREAS

(With the Exception of Functioning Islet-cell Adenoma)

Definition —For clinical purposes the similarity of diagnostic problems places certain nonneoplastic tumors such as pseudocysts parasitic cysts and hypertrophic pancreopathies together with the benign neoplasms in a group which is called the benign tumors of the pancreas The word tumor is employed synonymously with a mass as is customary in clinical language

The diagnostic evaluation of any mass or disorder of the upper abdomen must take a benign pancreatic tumor into consideration as one of the less common possibilities The incidence of benign pancreatic neoplasms is low even at autopsy e g 0 08 per cent for nonislet tumor[1] 0 12 per cent for islet tumors (benign) 0 04 per cent for true cysts[2]

Classification Anatomy Histology —The following classification reflects the variety of structures involved and presents the anatomy and histology Almost all types of benign neoplasms are found in the pancreas Non neoplastic enlargements are included in the clinical classification as mentioned above

I SOLID TUMORS

The solid neoplasms are usually small but occasionally reach a diameter of 8 or even 17 cm[4-7]

1 Lipoma
2 Fibroma papilloma polyp
3 Adenoma (encapsulated) fibro-adenoma
4 Myoma (deriving from muscles in ducts or vessel)
5 Cavernous hemangioma cavernous or solid endothelioma peri thelioma lymphangioma
6 Chondroma myxoma
7 Melanoma
8 Insuloma
9 Accessory pancreas in the ampulla or its vicinity (p 392)
10 Granuloma
11 Enlarged lymph node in the head of the pancreas
12 Hypertrophic chronic pancreopathy (p 493)

II CYSTS

A Small cysts
1 Congenital fibrocystic disease
2 Congenital polycystic disease[8 21]
3 Retention cyst in the course of chronic obstruction of the pan creatic ducts

Cysts which extend to the bile ducts and cause icterus are rare (5 to 10 per cent)[10,11] as are cysts which obstruct the pancreatic duct and cause specific pancreatic symptoms. Increase of serum amylase and/or lipase are occasionally encountered in such obstructing cysts. This occurs more often in pseudocysts. Hypoamylasemia occurs in advanced atrophy. Glycosuria is found in 5 to 8 per cent of the cysts.[11,12] It indicates advanced pancreatic atrophy provided that pre-existent diabetes can be ruled out. Pancreatic hypersalivation and a peculiar bronzing of the skin have also

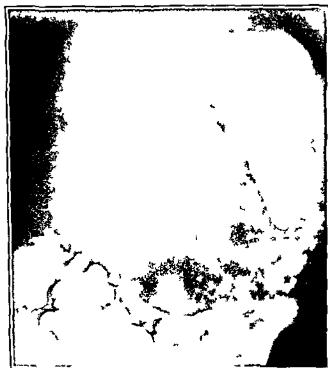


Fig 154 — Pancreatic cyst (large size) with widening of the duodenal loop and displacement of stomach, duodenum and adjacent small and large intestines

been reported.[9] Loss of weight, asthenia and listlessness may be encountered notwithstanding the benign nature of the cyst for reasons already mentioned. Yet such manifestations must always raise the question of malignancy.

The roentgen diagnosis is discussed on page 448 and 453.

In contrast to solid tumor the diagnosis of the cystic nature is sometimes possible by consideration of the etiology as follows (1) Echinococcic cyst is indicated by ring shaped calcifications, cysts in lungs or liver, blood eosinophilia and specific skin and serum tests. (2) Cysts of polycystic

5 Hyperinsulinism in the first phase of obstructive damage to the islets diabetes in the second phase

6 Hyperenzymemia or hypo-enzymemia (rare)

c *Signs of a Benign Disease* —The aforementioned manifestations of benign pancreatic tumors are in principle the same as in malignant tumors The diagnostic differentiation lies in the presence of normal weight sedimentation rate and blood count slow progress or no progress at all Occasionally loss of weight is caused also by benign tumors [14, 2] However malignancy should be excluded only when there is an obvious reason for benign loss of weight such as anorexia hyperemesis diarrhea or steatorrhea A large mass as a rule suggests a benign lesion

Diagnosis —The manifestations of a benign pancreatic tumor appear in three combinations of different diagnostic significance

Mass Plus Dysfunction —This syndrome is diagnostically significant but rare It is not conclusive in the differentiation between a mass of the pancreas or a mass in the vicinity involving the pancreas

Mass Without Dysfunction —When physical or roentgenologic signs of a mass in the epigastrium are either absolutely silent or associated with nonspecific digestive symptoms then the diagnosis rests on the exclusion of a disease in the vicinity and upon roentgenologic localization of the tumor in the pancreas

Dysfunction Without Mass —Some small obstructing tumors simulate a nonneoplastic chronic pancreopathy In order to find at least the larger of these tumors it is necessary *to examine every case of chronic pancreopathy roentgenologically for localized or diffuse enlargements of the pancreas*

After localization of a tumor in the pancreas the signs of a *benign* disease must be assured In the presence of a mass laparotomy is necessary Early surgery is safer than waiting for signs of malignancy

PANCREATIC CYSTS

The cysts of the group with potentially large tumors (groups 4 to 7) are the most frequent among the clinically manifest benign tumors The cysts follow the general pattern of the benign tumors However some details require special discussion There are cysts and pseudocysts

Cysts —The true cysts are lined by epithelium and contain from a few milliliters to 3 liters of fluid in exceptional cases up to 22 liters Presence of pancreatic enzymes characterizes a cyst of questionable origin as pancreatic Absence does not rule it out because the cyst may be lined by nonsecreting ductal epithelium or by a formerly secreting but atrophied epithelium Contrary to widespread opinion the mass may present considerable respiratory and palpatory mobility even from the right to the left epigastrium [9] The mass as a rule is firm Only the rounded shape and the smooth surface may then suggest the cystic nature Compressibility and fluctuation signs can be elicited in a minority of case In some cases the tumor is palpated below the umbilicus (See p 453)

Chills fever and leukocytosis occur with stasis infection and suppuration within the pancreatic ducts or the cyst

BIBLIOGRAPHY

1 SPROUL E E Quoted by Bockus in Reference 2
2 BOCKUS H L Gastroenterology Philadelphia Saunders Vol 3 p 808 1946
3 HALE WHITE W Diseases of Pancreas Guys Hosp R p 4 17 1897
4 LOTYA L Resection of First Size Lentil thoma of the Head of the Pancreas Zentrall Chir 48 08 1921
HABERER H VON Benign Solid Neoplasms of the Pancreas Arch f klin Chir 1 8 398 192
6 LRIE LI A Unusual Tumor of the Pancreas Virchows Arch f path Anat 354 1928
7 CRO F Small Cystic Adenoma of the Pancreas Frankfurt Zt hr f Path 3 3 0 1939
8 CARTER R F and SLATTERY I Cystadenomata of the Pancreas Am J Digest Dis 3 0 1936
9 BRUNSCHWIG A The Surgery of Pancreatic Tumors St Louis Mosby 1942
10 TAKAYA HU M Surgery of the Pancreas Mitt a d Grenzgeb d Med u Chir 3 83 1898
11 MUELLER H Surgery of the Pancreas Arch f klin Chir 143 285 1926
12 KOERTE W Surgical Diseases and Injuries of the Pancreas Deutsche Chirurgie edited by E von Bergmann and P von Bruns Stuttgart F Enke Vol 45 1898
13 FELMAN R and LIEBERMAN Z H The Pancreas Gastroenterology 21 24 195
14 HALKOHL R S and MELAMED A Cystadenoma of the Pancreas Am J Roentgenol 63 234 1950
15 COLLINS D L Pseudocysts of the Pancreas Arch Surg 61 3 1 0
16 SAYPOL G M Indications for Surgery in Diseases of the Biliary Tract and Pancreas New York S Med 51 16 1951
17 COLE W H Textbook of General Surgery 5th ed New York Appleton Century Crofts 1948
18 INVERFIELD I ANCRIST A and BENJAMIN J W The Antithrombin Titer in Pancreatic Cysts Am J Surg 83 8 1952
19 RHOAD J E HOWARD J M and MO M H Symposium on Surgical Physiology Clinical Experience with Surgical Lesions of the Pancreas Surg Clin North America 9 1801 1949
20 RALL J E and ODEL H M Congenital Polycystic Disease of the Kidneys Am J M Sc 18 399 1949
21 COMFORT M W GRAY H K DAHLIN D C and WHITTELL I B Polycystic Disease of the Liver Gastroenterology 0 60 1952
22 COHN R and GREENE W Cystadenoma of the Pancreas Stanford M Bull 8 27 19 0
23 CATTELL R B and WARREN K W Surgery of the Pancreas Philadelphia Saunders 1953

degeneration may be indicated by associated cystic disease of the liver and/or the kidneys[20, 1] (3) Dermoid cyst may be recognized by characteristic inclusions on a roentgenogram (4) Solitary cyst or cystadenoma may be assumed in the absence of such clues

Pseudocysts —Pseudocysts are located within the pancreas attached to the pancreas or separated in the lesser sac A pseudocyst is suspected when a mass develops within a few days or in a longer interval after an acute abdominal disease penetrating or not penetrating abdominal trauma[13] or general infectious disease especially when the disorders were accompanied by epigastric pain vomiting shock and elevated serum amylase A pseudocyst has been removed twenty years after the trauma[15] Fever leukocytosis and spontaneous or induced hyperenzymemia or glycosuria add weight to the diagnosis Pseudocysts may grow to contain more than 1 liter of fluid The content is either clear or more often hemorrhagic and cloudy by suppuration As a rule it contains pancreatic enzymes unless the cyst is very old The course is either nonprogressive for some time or there may be abscess formation or perforation Perforation may occur into stomach or intestines resulting in an internal pancreatic fistula which is usually transitory and leads to spontaneous cure Perforation also may occur into the peritoneal cavity or cause an external pancreatic fistula (p 503) Roentgenologic examination may show a mass After internal perforation there may be shown a fluid level and possibly an internal fistula Pancreatic enzymes in the fluid obtained from a questionable cyst at operation corroborate the pancreatic origin

MANAGEMENT OF BENIGN TUMORS

The etiologic management is surgical Solid tumors as well as cysts which are incidental findings at laparotomy should be excised if circumstances permit no matter how small they are The reasons are (1) to obtain a histologic diagnosis and (2) to prevent suppuration of fluid further growth and malignant degeneration For operative technic and further details on benign tumors see references 8 9 23 Of 8 patients who had elevated serum antithrombin preoperatively 6 maintained the elevation following surgery which may indicate that the obstruction or other damage was not completely removed[18]

Pseudocysts are best treated by total excision If this is impossible it is recommended that there be an anastomosis to the upper jejunum or duodenum (cyst enterostomy) If necessary the anastomosis can be made to the stomach (cyst gastrostomy) A pseudocyst has been removed 20 years after the trauma[1]

Retention cysts and *cystic adenomas* are treated by excision the latter requiring partial (left) pancreatectomy to prevent recurrence or malignant transformation[17, 19]

Benson and Cordon collected 28 reported cases of cystadenoma that were explored surgically Complete excision was done in 21 cases with an operative mortality of 20 per cent Large cysts *e g* pseudocysts and hydatid cysts are sometimes marsupialized in one stage operations or when suppurative in two stages[17, 19] This is a procedure of second choice but has less risk See also reference 23

Medullary gelatinous carcinomas are rare sarcomas extremely rare They are highly vascularized and tend to cause adhesions which make removal difficult

GROSS ANATOMY —The neoplasms appear as (1) nodes well demarcated either single or more often multiple bulging or buried in the tissue (2) Diffuse infiltration (3) Retracted scar rock hard and gritty on section

SITE OF THE TUMORS —The size and site of the tumor—particularly the site—determine the clinical features and the operability as follows

1 *Tumor of the Ampullar Region* —These neoplasms arise from the mucosa of the duodenum near the papilla or from the mucosa inside the ampulla and the lower ends of the ducts[10] or from aberrant pancreatic tissue in the papillary area The new growth may be papillar polypoid a a solid mass a flat ulcer with elevated hard nodular edges or scirrhous Malignant melanoma and sarcoma are exceptional findings At operation the size varies between a few millimeters and 3 cm They spread into the walls of the duodenum pancreatic duct and common duct and into the tissue of the head of the pancreas but they do not cause early remote metastases Tumors of the ampullar region soon exhibit gall bladder distention and icterus and permit early diagnosis

2 *Tumor Involving the Head of the Pancreas* —These neoplasms are more frequent than those of the ampullar region At necropsy in about 70 per cent of pancreatic carcinomas the head is involved either primarily or secondarily The relative incidence at operation is even higher because carcinomas in the head are diagnosed and consequently operated upon more frequently than carcinomas of the body Carcinomas of the head are said to have less tendency to spread locally or to metastasize than carcinomas originating in the body[6] however they tend to spread along the duct (cattel)

3 *Tumor Originating in the Body and Tail* —This location comprises 10 to 25 per cent of pancreatic carcinomas They often leave unaffected a portion of the pancreas between tumor and papilla which provides sufficient functioning tissue These tumors reach a considerable size before they can be diagnosed

4 *Diffuse Tumor* —Diffuse pancreatic involvement by infiltration scirrhous or numerous multiple nodes in all parts is reported in about 15 to 20 per cent of pancreatic carcinomas

SEQUELAE —They are as follows

1 *Pancreatic Obstruction* —The high incidence of the ductal type of pancreatic adenocarcinoma explains the high frequency of ductal involvement The obstruction may be caused not only by tumor masses but also by edema At autopsy ducts have been found patent where in life complete obstruction had been established The tissue alterations in pancreatic obstruction are outlined on page 494 and in reference 114 The islets may undergo the first obstructive phase of hyperfunction (p 409) but reach the destructive phase more rapidly than in other obstructions There are not infrequently interposed attacks of mild or severe enzymatic pancreopathy Clinically these are often missed

2 *Pancreatic Destruction* —Atrophy of acinar tissue develops in the suprastenotic area and on the site of neoplastic tissue

Chapter 28

THE MALIGNANT DISEASES OF THE PANCREAS

In the past decade clinical interest in the malignant diseases of the pancreas has been increasing The diagnosis has been improved by broader knowledge of the symptomatology and by advancement of the laboratory tests including roentgen examination Above all these previously intractable diseases in part have become subject to surgical therapy

Incidence —Pancreatic malignancy is not a frequent disease being encountered in about 0 3 to 0 75 per cent of autopsies [11] and between 1 and 4 8 per cent of all carcinomas in various statistics [1,6,8,9,11] Among the malignancies of the pancreas carcinoma is by far the most frequent

Age and Sex —As a rule carcinoma of the pancreas is a disease of the fifth to seventh decade It may occur earlier Nine cases of patients under twenty years of age are on record the youngest seven months old [2] Males are affected two to four times as often as females [86] white persons more frequently than Negroes The sex difference is less marked in the carcinoma of the ampulla

Pathology —Classification —The following types of malignant neoplasms may be classified [12]

A Carcinoma
  1 Ductal-cell adenocarcinoma
  2 Acinar cell adenocarcinoma
  3 Cystadenocarcinoma
  4 Squamous-cell carcinoma
  5 Scirrhous carcinoma
  6 Medullary carcinoma
  7 Gelatinous carcinoma
  8 Islet-cell carcinoma (p 548)
B Sarcoma
  1 Fibrosarcoma (spindle cell)
  2 Angiosarcoma
  3 Leiomyosarcoma
  4 Lymphosarcoma
C Carcinosarcoma
D Secondary (metastatic) carcinoma

Histology — Ductal -cell adenocarcinomas represent the majority (about 80 per cent) of pancreatic carcinomas The cells are cylindric columnar arranged in alveoli papillary cysts or simple cysts The intracellular connective tissue is often so prolific that a scirrhous carcinoma results Acinar -cell adenocarcinomas (about 20 per cent) consist of small cells of cuboidal oval triangular or polyhedral shape The malignant cells contain zymogenic granules and enzymes only occasionally [4,5,33,34]

ful but those of the head are by no means always painless. *Pain is the most important symptom* because of its early appearance, frequency, intensity and its subjective predominance among the manifestations. It is the complaint that brings most of these patients to the doctor for medical examination. All locations and types of pancreatic pain mentioned on page 117 may occur, of agonizing or very mild intensity. The pain is more or less constant, although with paroxysmal increases at times. It may occur as night pain. Increase of pain in the recumbent position, when the weight of the tumor presses upon the preaortic plexus, is characteristic. Such pain may wake the patient from sleep when he turns on his back.[2]

TABLE 4[illegible].—INCIDENCE OF SYMPTOMS IN CARCINOMA OF THE PANCREAS

8[illegible]% Pain		
87% Loss of weight		
65 to [illegible]5% Icterus	6–40% early cases	
	40% cancer of body	
	80% cancer of head	
[illegible]0% Weakness, fatigue		
[illegible]0% Courvoisier gallbladder	8[illegible]% in icteric cases	
	3[illegible]% in anicteric cases	
44% Anorexia		
3[illegible]% Constipation		
3[illegible]% Vomiting		
34% Nausea		
30% Diarrhea	11% in other statistics	
30%	Thrombophlebitis	16% cancer of head
		[illegible]1% cancer of body
2[illegible]%	Splenomegaly	
15%	Ascites preoperatively; 35% at autopsy	
12%	Palpable mass; 3[illegible]% in other statistics	
10%	Chyluria	
10%	Steatorrhea	
[illegible]%	Acute cholecystitis	
[illegible]%	[illegible]	

Sitting up, bending forward, doubling up or standing may give relief. A low thoracic girdle pain may simulate typical ulcer rhythm (in 12 per cent[2]), biliary colic or gastric crises. The pain may be like heartburn, a bloating gas pain or a very misleading lower or generalized abdominal pain. At the onset of the disease or at the first admission to the hospital the traditional painless jaundice was present only in 9–2[illegible] per cent of the cases.

Loss of Weight.—This also is an early and frequent sign, but as a rule longer overlooked than pain and icterus. The patient may lose a hundred pounds in six months.[1] The syndrome of weight loss associated with the pain of pancreatic type without other reasons of weight loss forms the

3 *Biliary Obstruction* —Malignancies in the ampullar region or head of the pancreas as well as enlarged periductal lymph nodes sooner or later lead to obstruction of the common bile duct The first consequence is a *Courvoisier gall bladder* owing to overfilling and dilatation (p 572) In a functioning gall bladder the overfilling is compensated for by absorption and excessive concentration of the bile This process delays the onset of icterus for a while but the excessive concentration of bile acids damages the wall of the gall bladder Thus the second consequence is *acute cholecystitis* which often is surgical and the first symptom in 10 per cent of pancreatic carcinomas Primarily it is a chemical aseptic cholecystitis Secondary infection frequently follows The third consequence is *mechanical icterus* which increases rapidly and soon is associated with complete absence of bile from the intestines The dilatation of the extrahepatic and intrahepatic bile ducts is greater than in other kinds of biliary obstruction Secondary *cholangitis* and cholangiolitis are not infrequent

4 *Hepatomegaly* —Pancreatogenic deficiency of lipotropic substances may cause fatty infiltration The biliary obstruction may cause obstructive enlargement of the liver and liver damage

5 *Obstruction of the splenic vein* resulting in splenomegaly ascites and thromboses

6 *Metastatic Spread*[6-11]—Metastases occur by four routes (1) Direct extension within the pancreas* and towards the common bile duct, stomach duodenum retropancreatic nerve plexuses splenic vein spleen and peritoneum (2) Lymphatic spread into subpyloric lymph nodes liver mediastinal peribronchial and even cervical lymph nodes (3) Hematogenous spread by the splenic or portal veins In some cases the metastatic tumor cells carry zymogenic granules and the metastases cause fat necroses [33]

Etiology —The majority of pancreatic carcinomas (80 per cent) derive from the ductal epithelium on the basis of an inherent tendency to malignant growth or on the basis of long standing ductal disease such as pancreolithiasis and other chronic pancreopathies which cause proliferation and metaplasia of the ductal epithelium Carcinogenic substances and vitamin A deficiencies also may initiate such metaplasia The acinar epithelium has less tendency to malignant degeneration Certain irritating factors favor carcinoma in the head of the pancreas Damage causing or following diabetes must be responsible for the higher incidence of pancreatic cancer in diabetics Malignant degeneration of a benign cystadenoma also is possible

Clinical Features —*In early cases the incidence of the main symptoms* is less than later 50 per cent pain without icterus 22 per cent pain with icterus and 18 per cent painless icterus

The incidence of symptoms and signs in *early and late* carcinoma [6, 11-14] is indicated in Table 45

Pain —In pancreatic carcinoma pain is caused by (1) carcinomatous invasion of nerve sheaths and ganglia (2) by pressure upon them and (3) by obstruction of the ducts [24] The carcinomas of the body are often pain

* Especially along the ducts

unknown to the patient begins with the development of the carcinoma Pre-existent constipation suddenly may become aggravated

Hematemesis Melena or Occult Hemorrhage —This is found in about one fourth of the cases It may be fatal The mechanisms may be (1) Carcinomatous ulcer or papilloma at the orifice or in the ampulla (2) Hemorrhage from highly vascularized ductal adenocarcinoma The ducts deliver 400 to 800 ml pancreatic juice daily thus they are capable of passing amounts of blood which cause tarry stools Such ductal hemorrhages may be associated with attacks of colicky pain fever and chills [24] (3) Varicose veins in stomach duodenum or esophagus resulting from tumor pressure (4) Carcinomatous invasion and ulceration of the gastric mucosa (5) Cholemic hemorrhage in icteric cases (6) In some cases the source of the hemorrhage could not be found as in some other intestinal hemorrhages

Chills and Fever —In addition to the above mentioned intraductal hemorrhage and acute cholecystitis chills and fever may be caused by infectious pancreodochitis and/or cholangitis chronic cholecystitis and abscess formation These symptoms *divert the diagnosis erroneously* from malignancy to an infectious inflammatory disease

Specific Pancreatic Symptoms —*Steatorrhea creatorrhea* and *diabetes mellitus* are characteristic but rare (10 per cent) and late [11,12] See laboratory findings on page 572

Thrombophlebitis —Monophlebitis polyphlebitis or migratory phlebitis seem to be more frequent and more marked than in other malignancies It has been reported in 19 per cent of carcinoma of the head and 56 per cent of carcinoma of the body and tail [21] but not in carcinoma of the ampulla [77] This difference indicates involvement of the splenic vein by stasis or invasion [1,2,1] The diagnostic value of associated phlebitis has been questioned [56]

Psychotic Symptoms —In recent years attention has been called to the fact that the first manifestations of pancreatic carcinoma may be psychiatric symptoms These may also develop later in the course of the disease Such patients have been sent to mental institutions which now have become conscious of pancreatic carcinoma as they became conscious before of another pancreatic disease the insulinogenic psychic disorders It is conceivable that hyperinsulinism plays a role in the psychic disorders of carcinoma which *obstruct the duct* *The manifestations vary from* anxiety to insomnia crying spell severe intractable depression and conviction of imminent death [1,6,17,1]

Signs of Malignancy —There is no early and definite clinical sign of malignancy Palpable metastases in liver pelvis inguinal umbilical or cervical lymph nodes are late Clinical clues are rapid loss of weight associated with pallor and weakness rapid progress of pain and of icterus a palpable mass and intestinal hemorrhage

The syndrome of *unexplained intestinal hemorrhage with ascites* is rather suspicious of malignancy although occasionally it is seen also in benign pancreatic tumor (see p 561) and especially in hepatic cirrhosis Swelling of the right face and neck owing to enlarged lymph nodes was the first sign of an occult malignancy which turned out to be a pancreatic carcinoma [33] The proteins of metastases can

largest group of early cases The syndromes of weight loss associated with anorexia hyperemesis or diarrhea are ambiguous and found also in nonmalignant chronic pancreopathies *Silent* weight loss is not infrequent It raises the suspicion of an occult malignancy with pancreatic carcinoma a foremost possibility Weight loss may be absent for some time especially in ampullary carcinoma and in obstructive carcinoma associated with hyperinsulinism It would be wrong to postpone an exploratory laparotomy just because there was no weight loss *Fatigue* is a frequent complaint

Icterus —This is the third of the three frequent manifestations (65 per cent)[11] It was an early symptom in only 6 per cent of 100 cases of pancreatic carcinoma[14] It is usually the first symptom in carcinoma of the ampulla and in those tumors of the head which involve the periampullar region In more distant carcinomas of the head and especially those of body and tail weeks or months elapse before the onset of icterus[5] Icterus also is a frequent reason why the victim seeks medical advice The usually severe itching involves much suffering Contrary to a long traditional opinion *icterus associated with pain* is much *more frequent* than the painless icterus Some authors[8] mention less than one fourth of the icteric cases as painless others give higher figures As a rule the icterus rapidly becomes very deep and the stool acholic Then the icterus is constant but in some cases intermittent It may even completely disappear for a while owing to regression of an obstructive edema or sloughing of an obstructing portion of the tumor However fluctuations of the icterus do not occur as rapidly as in obstructions by common-duct stone Obstruction of the bile duct and icterus are less marked and less frequent in carcinoma of the ampulla than in carcinoma of the head[67]

Absence of icterus does not rule out the diagnosis of pancreatic carcinoma Even cancers of the head were anicteric in 20 per cent of the cases This happens when the tumor originates in the lower portion of the head especially the uncinate process and grows downward[18]

Preicteric Acute Cholecystitis —In about 9 per cent of pancreatic carcinomas the illness begins with an acute surgical cholecystitis (p 568) Consequently *among the causes of a first attack of acute cholecystitis a pancreatic carcinoma* must be taken into consideration (See p 123)

Nonspecific Gastro-intestinal Symptoms (p 417) —These may be caused by (1) reflexes (2) dislocation stenosis or venous congestion of adjacent intestines and (3) invasion of intestines *Anorexia nausea vomiting* are frequent (60%)[80]* and early symptoms beginning simultaneously with the pain or shortly thereafter Hiccough has been described as a result of subdiaphragmatic lymph nodes *Hyperemesis* occurs in obstruction of the stomach or duodenum and is a symptom of advanced growth Nonsteatorrheic diarrhea intermittent or persistent is more frequent than steatorrhea which is less frequent in ampullary carcinoma (18 per cent) than in the more completely obstructing carcinoma of the head of the pancreas (46 per cent)[56] Steatorrhea develops when both the main and the accessory duct are not functioning as in large carcinoma of the head It occurs often enough to warrant a *suspicion of pancreatic carcinoma in unexplained diarrhea of elderly people*[19] More often a *constipation* hitherto

* 34 44 per cent in other statistics

Serum Amylase and Serum Lipase.—Bockus and his co-workers[25] have established three periods (1) Preobstructive period with normal serum enzymes (2) Obstructive period and functioning acinar cells with increased serum enzymes The increase is permanent or intermittent provoked by sudden floods of pancreatic juice following rich food or secretin injection The focal pancreatic necroses found in many necropsies of pancreatic carcinoma also are a potential source of hyperenzymemia (3) Obstructive period with functional inhibition or atrophy of acinar cells or replacement by the neoplasm and subsequently subnormal values of the serum enzymes

The *serum amylase* is elevated in about 50 per cent of the pancreatic carcinomas [6-9,34] the *serum lipase* in 33 to 66 per cent Amylase *and* lipase are increased simultaneously in 30 per cent of the cases [6,28 to 31] Normal values may be expected in the first or third of the aforementioned periods and in the second period during intermittence of the obstruction or

TABLE 46.—INCIDENCE OF LABORATORY FINDINGS IN CARCINOMA OF THE PANCREAS

Incidence	Finding
86- 8%	Diabetic glucose tolerance
80-45%	Roentgenologic Findings
6-32%	Anemia
66-36%	Hyperlipasemia
60-2 %	Hyperglycemia
50%	Hyperamylasemia
50%	Hyperantithrombinemia
27%	Occult intestinal hemorrhage 82% in ampullary carcinoma[20]
? -9%	Glycosuria { 7% prec i tel t; 40% advanced cases }
10-4%	Steatorrhea

during low pancreatic stimulation as the result of anorexia * The amylase may return to normal values before the lipase This and the differences in the standardization of the upper limit of normal values are reasons why some authors attribute a higher diagnostic value to the serum lipase

To sum up in the search for pancreatic cancer it is worthwhile to check the serum enzymes at frequent intervals Abnormal values direct the diagnosis to the pancreas Normal values do not rule out cancer of the pancreas

Serum Antithrombin It is increased as an obstructive phenomenon within the first weeks of jaundice in 50 per cent of the cases After that the serum level is normal or subnormal Only 1 per cent of nonpancreatic cancers show an increase[35]

Secretin Serum Enzyme Tests These were positive in several cases of pancreatic carcinoma[9]

Secretin Pain Test.—Provocation of the pain by injection of secretin is helpful in locating the seat of the pain (See p 4 6)

Bile in Duodenal Content.—Complete and constant acholia established in repeated examination is most suggestive of a malignancy in the vicinity

O 1 is tr me l truct as ul d presses the secretion of enzymes

induce an allergic response of the tissues manifested by polyarthritis and erythema nodosum.[24] Bone metastases cause skeletal symptoms.

In addition to weight loss, pallor, icterus, objective support of the diagnosis may be obtained by the following physical findings:

Palpable Mass in the Epigastrium.—In 12 to 37 per cent of pancreatic carcinomas a deep-seated firm mass of indefinite outline, pulsating in front of the aorta, can be palpated. It is at times definitely movable.[12] The mass represents the tumor itself or metastases in its vicinity.

Enlarged Liver.—Hepatomegaly is not infrequent (75 per cent).[11] It may be caused by (1) bile stasis, cholangitis, (2) fatty metamorphosis due to pancreatogenic deficiency of lipotropic substances, (3) liver metastases, central (smooth surface) or superficial (nodular surface). Superficial metastases are at times highly vascularized, pulsating, and associated with a bruit.[4] Metastases can be simulated by palpable distention cysts in the liver.[86]

Courvoisier Gall Bladder.—A distended gall bladder was found at necropsy in 87 per cent of the icteric cases and in 67 per cent of the total number of cases[6] at clinical examination in 50 to 70 per cent of the *icteric* cases[1,6,18] and in 37 per cent of *anicteric* cases. Injection of a short-acting barbiturate or examination in a warm bath facilitates the palpation of the Courvoisier gall bladder.

The palpable gall bladder of pancreatic carcinoma requires differentiation from (1) benign common-duct obstruction, (2) cystic-duct obstruction resulting in hydrops or empyema, (3) gall bladder filled with stones, (4) carcinoma of the gall bladder, and (5) extravesicular mass (omentum, kidney, hypernephroma, pancreatic cyst, etc.). The enlarged gall bladder is often displaced to the right.

Absence of a palpable gall bladder in icteric cases of pancreatic carcinoma may be expected as the result of (1) unfavorable conditions for palpation, such as large liver, and (2) shrunken gall bladder, e.g., when pancreatic carcinoma develops in cases of long-standing chronic cholecystitis with cholelithiasis.

Splenomegaly (25 per cent).—This is caused by compression or thrombosis of the splenic vein.[15]

Ascites.—It is rare. It may be the result of (1) thrombophlebitis in the pancreatic veins and/or the portal vein, (2) compression of the portal vein by the tumor or lymph nodes, (3) peritoneal metastases, and (4) hypoproteinemia.

To summarize the data on clinical features, there are a number of cases which present nothing but *pain* or *pain plus weight loss* for a long period of time.

Laboratory Findings.—Clinical findings, as a rule, require confirmation by roentgenologic (see p. 454) and other laboratory tests which have become more elaborate and helpful than they were ten years ago. If there is any doubt, repetition at very short intervals is necessary. *Negative laboratory tests should not overrule a well founded clinical suspicion and must never delay a possibly lifesaving laparotomy.* The incidence of the laboratory findings is reported in Table 46.

The diagnostic evaluation of the *duodenal tests* is as follows

1 Normal findings do not rule out pancreatic carcinoma They are encountered in the preobstructive phase in incomplete obstruction or when the obstruction is in the tail 2 Abnormal findings are most useful in locating the disease in the pancreas 3 Low volume in the secretin test [7 37 40 42] and the mecholyl test [0 30] is very suspicious of pancreatic malignancy when clues for an atrophic disease benign obstruction or technical errors are absent The volume sometimes was reduced to a few milliliters especially in carcinoma of the head *Low volume and normal concentration* indicate an obstruction which cuts out enough tissue to reduce the volume but leaves enough functioning pancreatic tissue to maintain the concentration in the duodenal content within normal limits *Low volume and low concentrations* indicate either proximal obstruction or deficient function of the nonobstructed pancreatic tissue e g destruction of acinar tissue by the neoplasm or carcinoma growing in a pre-existent atrophic pancreopathy 4 *Total absence of enzymes* (or almost total absence) indicates a large neoplasm in the head of the pancreas which has extended upon both the main and accessory ducts However atrophy in nonneoplastic chronic pancreopathy must be excluded The possibility of a congenital nonfunctioning accessory duct must also be taken into consideration

Cytology of Duodenal Content (Papanicolaou Test) —This is the most direct method (p 445) and rendered positive results in several cases of this clinic It should be used whenever pancreatic malignancy is suspected [37 9]

Steatorrhea and Creatorrhea —Manifest steatorrhea is found only in 4 to 10 per cent of pancreatic carcinomas Latent steatorrhea is disclosed more frequently e g by assimilation tests such as microscopic examination of the stool after Schmidt s test diet [8] In a suspected case regular findings of unusual amounts of undigested muscle fibers point to the pancreas when gastric anacidity and diarrhea are absent The normal loss of 15 *per cent nitrogen in the stools may rise to 40 per cent*

Acholic Stool and Absence of Urobilinogen in the Urine —This indicates complete obstruction of the bile duct and if persistent is suspicious of malignant obstruction

Diabetes Mellitus —Diabetic blood sugar curves in the glucose tolerance test are found in 86 to 75 per cent of pancreatic carcinoma They appear long before fasting hyperglycemia [14] and the latter appears long before glycosuria which is encountered in 40 per cent of advanced cases Berk calls the disturbance of the islets of Langerhans surprisingly frequent *but distressingly overlooked* *Diabetes beginning after the onset of signs* of an occult malignant neoplasm indicate its seat in the pancreas Preexistent diabetes does not rule out pancreatic carcinoma On the contrary with the 7 per cent incidence carcinoma of the pancreas is the most frequent malignancy of diabetics six to sixteen times as frequent as in the population at large Cancer of the pancreas has developed nine years after the onset of the diabetes [43-46] Some cases have excessive insulin resistance [33]

of the ampulla Incomplete or intermittent acholia may be due to benign as well as malignant causes Calculous obstruction as a rule is incomplete fluctuating and intermittent (p 570) Complete absence of bile was found less often in carcinoma of the ampulla (about 50 per cent) than in carcinoma of the head of the pancreas (about 93 per cent)

Blood in Duodenal Content —Gross hemorrhage in duodenal content is not infrequent in all types of pancreatic carcinoma (see p 571) It is suggestive when the more frequent causes of hemorrhage such as gastroduodenal ulcer cancer of the gastric or duodenal mucosa and cholemia can be ruled out The syndrome *posthepatic icterus-blood in duodenal content-diarrhea* is characteristic of ampullar carcinoma[41] Gross hemorrhage was found in 38 per cent of cancer of the ampulla and in 25 per cent of cancer of the head



FIG 135 —Inoperable carcinoma of head of pancreas with T tube drainage of common bile duct A Shows intrusion of the tumor into the lower common bile duct B Taken two months later shows further obstruction of the common bile duct and dilatation of the gall bladder and bile ducts

Small capillary bleedings and a considerable amount of microscopic blood as a rule are due to friable mucous lining violent gastric contractions and/or forced suction Nevertheless they must not to be ignored entirely when noted in all specimens and not preceded by the aforementioned factors

Pancreatic Constituents in Duodenal Content —Carcinoma in contrast to parenchymatous chronic pancreopathy does not cause diffuse functional damage unless it destroys almost the entire pancreas or causes marked obstruction In each of 15 cases of carcinoma of the head or body the secretin test revealed some pathologic reductions of pancreatic secretions[37] as follows

Volume	Total Amylase	Concentration of Amylase	Concentration of Bicarbonate
10	12	5	3

The diagnostic evaluation of the *duodenal tests* is as follows:

1. Normal findings do not rule out pancreatic carcinoma. They are encountered in the preobstructive phase, in incomplete obstruction or when the obstruction is in the tail. 2. Abnormal findings are most useful in locating the disease in the pancreas. 3. Low volume in the secretin test[7, 37, 40, 42] and the mecholyl test[9, 30] is very suspicious of pancreatic malignancy when clues for an atrophic disease, benign obstruction or technical errors are absent. The volume sometimes was reduced to a few milliliters, especially in carcinoma of the head. *Low volume and normal concentration* indicate an obstruction which cuts out enough tissue to reduce the volume but leaves enough functioning pancreatic tissue to maintain the concentration in the duodenal content within normal limits. *Low volume and low concentrations* indicate either proximal obstruction or deficient function of the nonobstructed pancreatic tissue, e.g., destruction of acinar tissue by the neoplasm or carcinoma growing in a pre-existent atrophic pancreopathy. 4. *Total absence of enzymes* (or almost total absence) indicates a large neoplasm in the head of the pancreas which has extended upon both the main and accessory ducts. However, atrophy in nonneoplastic chronic pancreopathy must be excluded. The possibility of a congenital nonfunctioning accessory duct must also be taken into consideration.

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Volume	Total Amylase	Concentration of Amylase	Concentration of Bicarbonate
10	12	5	3

Diagnosis.—*Suspicion of Pancreatic Malignancy*.—This can be raised by a great number of syndromes which may be classified in the anicteric and the icteric groups.

In *anicteric* cases the following syndromes suggest pancreatic carcinoma as one of the possibilities, especially when they occur between the ages of fifty and seventy after a short illness and without noticeable etiology. (1) The silent rapid loss of weight. (2) The occult neoplasm. (3) The unexplained (the roentgen negative) abdominal pain particularly when associated with loss of weight. (4) The unexplained anorexia. (5) Sudden onset of constipation or dyspepsia (gas syndrome). (6) The unexplained diarrhea. (7) Onset of steatorrhea without a history of acute or chronic

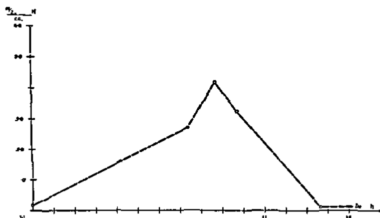


FIG 136.—Serial determination of serum lipase during the course of a carcinoma of the pancreas demonstrating (1) The negative pre-obstructive period. (2) The positive obstructive period. (3) The negative obstructive period which results from destruction of the acinar tissue. (Adapted from Johnson T A. *Postgraduate Gastroenterology* edited by H L Bockus p 314 Fig 153 Philadelphia W B Saunders & Co 1950.)

pancreopathy. (8) The unexplained melena or hematemesis (absence of gastro-intestinal ulceration and liver cirrhosis), the roentgen negative intestinal bleeding. (9) Diabetes mellitus starting in the critical age. Diabetes preceded by or associated with pain, loss of weight which exceeds the seventy of glycosuria, high sedimentation rate and anemia. (10) Acute cholecystitis without noticeable etiology (see p 570). (11) Failure to improve after cholecystectomy, i.e., persistent jaundice or development of an external biliary fistula.[2] (12) Charcot's fever associated with Courvoisier gall bladder. (13) Growth of an unidentified epigastric mass. (14) Phlebitis, polyphlebitis migratory phlebitis. (16) Nervous and psychotic symptoms. (See p. 571.)

In *icteric* cases the following syndromes raise the suspicion of pancreatic carcinoma. (1) Severe mechanical icterus with rapid development, rapid weight loss, high sedimentation rate and anemia. (2) Palpable gall

Blood Count —Severe anemia as a rule is not encountered in the early state[86] despite the frequent findings of blood in the duodenal content and stools

Serum Bilirubin Serum Cholesterol Serum Phosphatase —Posthepatic jaundice (p 375) fits well the diagnosis of pancreatic carcinoma as one of the possible causes In serial determinations the level of bilirubin does not show the frequent fluctuation seen in calculous obstruction although some change is possible (p 570) In 88 patients with resectable lesions the bilirubin was 1–10 mg per cent in 50 per cent of the cases from 10–20 mg per cent in 35 per cent from 20–33 mg per cent in 8 per cent[86] Serum phosphatase can be elevated also in anicteric pancreatic obstructions[38]

Liver Function Tests —After several weeks of icterus the cephalin flocculation and thymol turbidity test may become positive Then they are no longer of value in the exclusion of mechanical icterus Very valuable and necessary is the determination of the prothrombin level and its response to the administration of vitamin K[86]

Urobilinogen Output —Owing to the completeness of the obstruction the output of urobilinogen in feces and urine is more often and more markedly reduced in malignant obstruction than in calculous obstruction[46 47]

TABLE 47 —UROBILINOGEN OUTPUT IN MECHANICAL ICTERUS OWING TO NEOPLASM OR GALL STONE

Reduction of Output	*Per Cent of Cases with Neoplasm*	*Per Cent of Cases with Gall Stone*
In feces to less than 5 mg per twenty four hours	90	10
In urine to less than 0 3 mg per twenty four hours	90	10

Needle Biopsy of the Liver —The result may clarify the case when the needle happens to hit a carcinomatous metastasis

Occult Blood in Feces —This is found in 27 per cent of pancreatic cancer[6] In the absence of other sources of intestinal bleeding *e g* in the roentgen negative abdominal disorders a positive blood test suggests pancreatic malignancy as a possibility (see pp 571 and 574)

Signs of Malignancy —The syndrome *mechanical icterus* high *sedimentation rate* and severe *anemia* is very suggestive of malignancy which can be located in the common bile duct liver duodenum or head of the pancreas The syndrome—*diabetes high sedimentation rate* and *anemia*—must raise the suspicion of pancreatic malignancy

Gastroscopy —In certain cases gastroscopic examination can aid the diagnosis of pancreatic cancer by detecting malignant invasion of the gastric mucosa or gastric distortions[48]

Roentgenologic Examination —When properly specified technic is employed two thirds[1 36] to four fifths[14] of pancreatic carcinomas present positive roentgen signs at some period of the disease (see p 454 and references 86 and 89)

Improved intensified and repeated roentgenologic examination in conjunction with the pancreatic function tests facilitate an early diagnosis and furnish indications for surgery

Management.—Medical management is restricted to the preparation of the patient for surgery and to treatment of the operated upon and inoperable patients. Most of these require relief of pain as well as the substitutional exocrine and endocrine treatment which is outlined on pages 407 and 524 to 527.

The essential management is surgical, either radical or palliative. Unfortunately a great number of patients at the time of admission are not subjects for radical surgery,[9] because the cancer caused symptoms only after considerable growth. However there are still too many patients who miss early surgery because the suspicion of pancreatic carcinoma was not *raised or adequately checked in time. Only early suspicion and early exploratory laparotomy* by a surgeon who is experienced in the diagnosis at laparotomy as well as in the necessary decisions and technic make possible the radical operation which will improve the over-all result. Such improvement should be possible because even in patients who died from *pancreatic cancer 12 per cent had no metastases and an additional 5 per* cent had only local metastase.[77] Proper examination can be done within a week, during which time preparations for operation should be started, such as administration of vitamins B, C and K and blood transfusions for jaundiced patients.

It is of course most desirable to arrive at a definite preoperative diagnosis. However, in many cases laparotomy must be done on a clinical possibility of carcinoma of the pancreas. Whipple stated that the patients should not be studied to death before they reach the surgeon.

1. RADICAL SURGERY.—(*a*) *Carcinoma of the Ampulla.*

Transduodenal Excision.—An incision through the anterior wall of the second portion of the duodenum exposes the papilla major. Growths of limited size are excised by eliptic incision. The transected ducts are reimplanted. This operation was introduced by Halsted in 1898. The *operative mortality* is reported to be 46 per cent.[51] This figure is probably much reduced by elimination of terminal cases and improved preoperative and postoperative care of jaundiced patients. The result of excision is an *average survival of sixteen months*[51] compared with three to seven months *in those not operated upon.*[10, 53] *Occasional patients survived from 2 to* 5 years,[15] even 22 years.[52]

Pancreaticoduodenectomy in Carcinoma of the Ampulla.—The head of the pancreas cannot be removed without the duodenum because of the common blood supply. Occasional pancreaticoduodenectomies have been done since Billroth's *first reported operation in 1884.* The *recent advance* of pancreatic surgery in this field begins with the two-stage operation described by Whipple, Parsons and Mullins in 1935.[54] Since then the pancreatectomy has been developed further by Trimble, Parsons and Sherman,[55] Orr,[56] Pearse,[69] Cole and Reynolds[65] and others.

Nowadays and as a rule the pancreaticoduodenectomy is done as a one-stage operation, the two-stage operation with a four week interval being reserved for specified conditions.[6, 63, 77] For the physiological and nutri*tional status after total pancreatectomy* see page 407. The *operative mortality* has come down from 23 per cent to 11.8 per cent[67] and 5 per cent in special series. The *results* of pancreatectomy in *carcinoma of the*

bladder or epigastric mass (3) Pain in the *left* upper quadrant and signs of malignancy (4) Diabetes especially when of recent origin and accompanied by pain and signs of malignancy (5) Gastro intestinal *hemorrhage in the absence of another source of bleeding*

Presence of gastric or duodenal *ulcer cholelithiasis* or preceding *chronic pancreopathy do not rule out* coexistent pancreatic carcinoma [28 44] A *short history* of pancreatic symptoms in a man over fifty points to malignancy A *long history* e g of nine years duration does not rule out malignancy because carcinoma can grow out of (1) initially benign cystadenoma [49 50] (2) chronic pancreopathy just as primary carcinoma of the liver grows out of a cirrhotic liver [2 28] or (3) diabetic pancreopathy of four to nine years duration [28 44] At times it remains questionable whether it was a slow growing malignant tumor from the onset or a tumor superimposed upon a nonmalignant disease of the pancrea [8]

Verification of the Suspicion —It must be established (1) that the pancreas is the seat of the disease (by roentgen findings serum enzymes duodenal function tests and absence of nonpancreatic diseases) (2) that the nature of the pancreatic disease is probably or definitely malignant (high sedimentation rate anemia positive Papanicolaou test in duodenal content metastases in clinical or roentgenologic examination or liver needle biopsy)

In cases offering the afore mentioned verification a rather definite preoperative diagnosis of pancreatic carcinoma is possible

In the absence of these findings the preoperative diagnosis of pancreatic carcinoma remains just one of many possibilities For instance *in mechanical icterus it is often impossible to differentiate the causes preoperatively* (see p 375) Some common duct stones cause painless icterus and some pancreatic carcinomas cause acute cholecystitis (p 568) biliary colic intermittent jaundice or Charcot s fever The diagnostic uncertainty is enhanced by the fact that cholelithiasis and carcinoma of the pancreas can coexist However in most cases either the *possibility of abdominal malignancy* or the presence of *mechanical icterus requires laparotomy* leaving the definite differential diagnosis to the surgeon and to evidence shown in frozen sections *Such laparotomy must not be delayed* Too much is at stake to wait

Diagnosis at Surgical Exploration —Nodular as well as metastasizing carcinomas may be diagnosed with certainty A retracted scar or diffuse fibrosis of the head or the entire pancreas presenting either an enlarged or a contracted hard organ may simulate or conceal carcinoma and deceive not only *the surgeon but also the pathologist at microscopic examination* This happens not only in small biopsies but even in the pancreatectomy specimen [1 44] The interpretation of the findings and the value of the exploration depend largely on the experience of the surgeon [8] It must be admitted that there are limitations in evaluation of the macroscopic and microscopic examinations [1 80 83]

Diagnosis by Postoperative Course —The diagnosis of a nonmalignant disease may be corrected by a malignant course On the other hand cases which were diagnosed as malignancy at operation have been verified as nonmalignant fibrosis by a permanently benign course following a by passing operation

(4) ligation of pancreatic arteries in an attempt to slow down the growth of the neoplasms and (5) radiation therapy following palliative surgery *

Simple cholecystostomy in malignant pancreatic obstruction of the bile duct has an *operative mortality* of only 10 per cent [76] Short-circuiting operations are more effective but the mortality ranges from 20 to 40 per cent This figure will be much smaller when terminal cases are eliminated and modern preoperative and postoperative care of icteric patients is administered

The immediate result of palliative surgery is often excellent The decompression of the biliary tract brings relief from pain icterus pruritus and rapidly progressing liver damage Icterus is abolished at least temporarily in 96 per cent of the cases [75] Many patients gain weight and become able to take up their activities

The average *survival is ten months* as compared to from three to eight months duration in nonoperated cases Exceptional cases survived up to one and a half years and one case four years [1] Radiotherapy following palliative operations is indicated [1] For further information see references 1 and 80

The palliative operation was followed by cure in 10 to 20 per cent of the operations because the obstruction turned out to be benign [4, 74]

To sum up the outlook for some patients suffering from pancreatic carcinoma especially ampullar carcinoma is no longer absolutely hopeless as it was twenty years ago

* Cattel and Warren employ in certain cases a short circuiting operation for the supraduodenal pancreatic duct

BIBLIOGRAPHY

1 Brunschwig A *The Surgery of Pancreatic Tumors* St Louis Mosby 1942
2 Bockus H L *Gastroenterology* Chapter 118 by J E Berk Philadelphia Saunders 1946
3 Schnedorf J and Orr T G Fifty two of Forty Cases of Carcinoma of the Pancreas and Ampulla of Vater with Special Reference to Fatty Infiltration of the Liver Ann Surg 11 603 1941
4 Comfort M W Butt H R Baggenstoss A H O Terrer S J and Priestley J T Acinar Cell Cancer of Pancreas Ann Int Med 19 809 1943
Sugiura K Jack C and Stewart F Enzyme Content of a Pancreatic Islet Adenocarcinoma of the Pancreas and a Comparison with the Normal Human Pancreas Am J Cancer 8 3 1936
6 Berk J E Diagnosis of Carcinoma of the Pancreas Bockus H L *Gastroenterology* Philadelphia Saunders 1950
Rothenberg R and Aronson S Acute Cholecystitis Including Neoplastic Common Duct Obstruction Ann Surg 11 00 1940
8 Bigelow and Lord H *Carcinoma and Other Diseases of the Pancreas* Boston Houghton Mifflin 1933
9 Clute A The Problem of Carcinoma of the Pancreas J A M A 10 11 1936
10 Illber M Stewart H and Lund H Carcinoma of the Periampullary Portion of Duodenum Ann Surg 102 215 383 1939
11 Berk J E Diagnosis of Carcinoma of the Pancreas Arch Int Med 68 5 1941
12 Rives J Romano S and Sander F Carcinoma of the Pancreas Surg Gynec & Obst 6 164 1938
13 Silver G B and Liebliner R Carcinoma of the Pancreas Surg Gynec & Obst 56 03 1948
14 Broadbent T R and Kerman H D Carcinoma of the Pancreas Gastroenterology 1 163 1941
15 Duff G Carcinoma of the Body and Tail of the Pancreas Bull Johns Hopkins Hosp 6 61 1939

ampulla are encouraging A recent review of 35 such pancreatectomies which have been reported from 1942 to 1949[51] presents 37 per cent survivals of three years 29 per cent survivals of five years and 16 per cent cures (observation for five to seven years) Reoperation for recurrence following pancreatectomy has been successful in two thirds of the cases [52]

(*b*) *Carcinoma of the Pancreas* —This is treated by *pancreaticoduodenectomy* The operative mortality has come down from an initial 44 per cent[61] and 31 per cent[51] to 16.7 per cent[68] and 8.3 per cent[69] in special series Non operated cases have a life span of *four to eight* months The *results of pancreatectomy in carcinoma of the pancreas proper are discouraging* Out of a total of about 150 resections apparently only 5 patients[1,6,67,56] have been cured thus far They present a survival from five to eleven years However among the survivors with an observation period of less than five years there may be some more who later will add to the list of permanent cures For criteria and technics of radical surgery as well as preoperative and postoperative care see reference 56 The details are presented in Table 48

TABLE 48 —REVIEW OF THE RESULTS OF SURGERY REPORTED FROM 1942 TO 1949[51]

Site of Carcinoma	*Operation*	*Number of Cases*	*Operative Mortality per cent*	*Survival* *Average Months*	*Three Years per cent*	*Five to Seven Years per cent*
Ampulla	None		0	3–7		
	Excision	13	46	16	7.6	0.0
	Pancreatico-duodenectomy	35	23	23	37.1	28.6
Pancreas	None[5,27]		0	4–8	0.0	0.0
	Pancreatico-duodenectomy	42	31	13	6.9	3.3
	Cholecystostomy		10	10	Occasional	0.0
	Short circuiting[1]		30–50	10		

The number of cases in each group is less than 100 Percentage figures are used here only for preliminary comparison

Whipple[60] said in an editorial of 1951 that in contrast to the better results in carcinoma of the ampulla the pancreatectomies in carcinoma of the pancreas seem to be little more than a palliative measure Orr[56] emphasized that radical removal of cancer fulfills the requirements of cancer surgery in general and offers hope for a greater number of cures in the future when the operation can be done in earlier stages Cattell and Warren[6] say Total pancreatectomy gave poor results in advanced cases however it should be carefully evaluated for the early malignant lesion arising in the head of the pancreas

2 PALLIATIVE SURGERY —At laparotomy 25 to 30 per cent of the cases were not resectable In other cases the greater risks of radical surgery and the hitherto poor results in carcinoma of the pancreas proper cause preference for palliative procedures such as (1) cholecystostomy (2) short circuiting operations of the gall bladder or common duct for common-duct obstruction (3) short circuiting operations for gastroduodenal obstruction

47 WATSON C C Di eases of Gall Bladder an l Bile Ducts in *Textbook f Medicine* edited by R L. CECIL 6th ed l hiladelphia Saunders 1944
48 MOERSCH F and COMFORT M Gastroscoj y as an Aid in Diagno i f Pancreatic Cancer Am J Surg 6 423 19 0
49 LICHTENSTEIN L Lapill ry Cy tadenocarcinoma f the Pan r Am J Cancer 1 542 1934
50 YOUNG I JR Pancreatic Cyst New England J Med 16 334 133
51 LOGGAN P B and KLEINSASSER I J Surgery f the Pancreas Internat Al str Surg 93 521 1951
52 MULLER C and RADEMAKER L End Results in Radical Operations for Carcinoma of the Periampullar Region of the Duodenum Ann Surg 93 5 1931
53 OUTERBRIDGE G Carcinoma of the Papilla of Vater Ann Surg 402 1913
54 WHIPPLE A O PARSONS W B and MULLIN C R Treatment f Carcinoma of the Ampulla of Vater Ann Surg 10 63 1935
55 TRIMBLE I R PARSONS J W and SHERMAN C I A One-stage Operation for the Cure of Carcinoma of the Ampulla of Vater and Head of the Pancreas Surg Gynec & Obst 3 11 1941
56 ORR T C Resection of the Duodenum and Head of the Pancreas for Carcinoma of the Ampulla Surg Gynec & Obst 73 240 1941
57 ——— Pancreaticoduodenectomy for Carcinoma of the Ampulla and Ampullary Region Surgery 18 144 1945
58 REYNOLD J T and MARLOWE W Present Status of Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater and of the Head of the Pancreas J Internat Coll Surgeons 10 544 1947
59 PEARSE H E A Simplified Anastomosis for Resection of the Duodenum and Head of the Pancreas Surg Gynec & Obst 333 1942
60 BRUNSCHWIG A Resection of Head of the Pancreas and Duodenum for Carcinoma Pancreaticoduodenectomy Surg Gynec & Obst 6 681 193
61 CHILD C C Pancreaticojejunostomy and Other Problems Associated with the Surgical Management of Carcinoma Involving the Head of the Pancreas Ann Surg 11 845 1944
62 CHILD C G HOLSWADE C R MCCLURE R D CORE A J and O NEILL E A Pancreaticoduodenectomy with Resection of the Portal Vein in the Macaca Mulatta Monkey and in Man Surg Gynec & Obst 9 31 1952
63 CATTELL R Resection of the Pancreas Surg Clin North America 3 53 1944
64 ———B A Technique for Pancreatoduodenal Resection Surg Clin North America 8 61 1948
65 COLE W H and REYNOLDS J T Resection of the Duodenum and Head of the Pancreas for Primary Carcinoma of the Head of the Pancreas and Ampulla of Vater Surgery 18 133 1945
66 PERSON E C and GLENN F Pancreaticogastrostomy Arch Surg 39 5 0 1939
6 MILLER F M DOCKERTY M B WOLLAEGER E F and WAUGH J M Carcinoma in the Region of the Papilla of Vater Surg Gynec & Obst 92 1 2 1951
68 CATTELL R B and PYRTEK L J An Appraisal f Pancreatoduodenal Resection Ann Surg 1 9 840 1949
69 CHILD C G Radical One-stage Pancreaticoduodenectomy Surgery 3 840 1949
0 WHIPPLE A O Tumors of the Pancreas and Ampulla Editorial Surg Gynec & Obst 93 112 1951
1 JUDD L and HOERNER M Surgical Treatment of Carcinoma f the Head of the Pancreas and Ampulla of Vater Arch Surg 31 13 1935
2 RANSOM H C Carcinoma of the Body and Tail of the Pancreas Am J Surg 30 584 193
3 ——— Carcinoma f th r and E tral epatic Bil Duct Am J Surg 10 264 1938
4 WALTER W and CLEVELAND W H Surgical Lesions of the Pancreas Arch Surg 4 813 1941
WALTERS W and DEHNE I Jaundice Caused by Pancreatic Lesions Surg Gynec & Obst 4 839 1939
6 SALTZ K M A and CARLOCK J H Obstructive Jaundice Due to Carcinoma of the Pancreas Ann Surg 11 2 1949

16 YASKIN J C Nervous Symptoms as Earliest Manifestations of Carcinoma of the Pancreas J A M A 96 1664 1936
17 PELNER L Carcinoma of the Pancreas Gastroenterology, 8 92 1947
18 EUSTERMAN G and WILBUR D Primary Malignant Neoplasms of the Pancreas South M J 26 875 1933
19 FRIEDENWALD J and CULLEN T S Carcinoma of Pancreas Am J M Sc 176 31 1928
20 COOPER W Carcinoma of the Ampulla of Vater Ann Surg 106 1009 1937
21 SPROUL E E Carcinoma and Venous Thrombosis Am J Cancer 34 566 1938
22 UMLAUFT W Thrombosis and Cancer of the Pancreas Munchen med Wchnschr 80 607 1933
23 LEVY H and LICHTMAN S Primary Carcinoma of the Body and Tail of the Pancreas Arch Int Med 65 607 1940
24 RIML O Intestinal Hemorrhage for the Diagnosis of the Carcinoma of the Tail of the Pancreas Wien Arch f inn Med 32 21 1938
Differential Diagnosis of the Aneurysm of Intrahepatic Arteries Med Klin 2 974 1935
25 JOHNSON T A Value of Serum Amylase and Lipase Determination in the Diagnosis of Pancreatic Lesions in BOCKUS H L *Post Graduate Gastroenterology* Philadelphia Saunders p 310 1950
26 ELMAN R ARNESEN N and GRAHAM E A Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease Arch Surg 19 943 1929
27 LAGERLOF H O *Pancreatic Function and Pancreatic Disease Studied by Means of Secretin* New York Macmillan 1942
28 BAUMAN L *The Diagnosis of Pancreatic Disease* Philadelphia Lippincott 1949
29 MCCALL M L and REINHOLD J G Clinical Significance of Serum Amylase and Lipase Determinations Surg Gynec & Obst 80 434 1945
30 COMFORT M W and OSTERBERG A E Determination of Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas Proc Staff Meet Mayo Clin 15 42 1940
31 JOHNSON T A and BOCKUS H L Serum Lipase Test Am J Digest Dis 10 1 1943
32 BRUNSCHWIG A Re-operation Following Pancreatoduodenectomy Cancer 3 624 1950
33 EDELSTEIN J Pancreatic Carcinoma with Unusual Metastasis to Skin and Subcutaneous Tissues Simulating Cellulitis New England J Med 42 (?) 19?0
34 OSBORNE R Functioning Acinous Cell Carcinoma of Pancreas Accompanied with Widespread Focal Fat Necrosis Arch Int Med 85 933 1950
35 DAVIDSON J and EDELMAN E E Insulin Resistance Arch Int Med 86 2 1950
36 PIGOTT F Radiological Appearances in Pancreatic Cancer Brit J Radiol 3 656 1950
3 DREILING D A Pancreatic Function IV The Use of Secretin Test in the Diagnosis of Tumors In and About the Pancreas Gastroenterology 18 184 1951
38 NORTHMANN M H Effect of Ligation of Pancreatic Ducts of the Serum Phosphatase Proc Soc Exper Biol & Med 5 15 1944
39 LOFFSMAK M S and BOCKUS H L Study of Pancreatic Serum Enzymes Following Secretin Injection in Pancreatic Affection Gastroenterology 18 234 1950
40 DIAMOND J S and SIEGEL S A Secretin Test in Diagnosis of Pancreatic Diseases Am J Digest Dis ~ 435 1940
41 DENECHAU D TONCEY A and VARANCOT J Cancer of the Ampulla of Vater Bull méd Paris 45 535 1931
42 PRATT J H Pancreatic Disease New York State J Med 43 184 1943
43 MCKITTRICK L S and ROOT H F *Diabetic Surgery* Philadelphia Lea & Febiger 1928
44 BROCQ B and MICINIAC G *Surgery of the Pancreas* Paris Masson 1934
45 MARBLE A Diabetes and Cancer New England J Med 211 339 1934
46 SPARKMAN R Urobilinogen Clinical Value of Determination of Urobilinogen Content of Single Specimens of Urine and Stool Arch Int Med 63 872 1939

47 WATSON C G Di ases of Gall Bladder and Bile Du t in Textbook of Medicine edited by R L CECIL 6th ed Philad lphia Saunders 1944
48 MOERSCH F and COMFORT M Ca tro copy a an Aid in Diagnosis of Pancreatic Cancer Am J Surg 46 479 1950
49 LICHTENSTEIN I Papillary Cystadenocarcinoma f the P ncreas Am J Cancer 1 549 1934
50 YOUNG I JR Pancreatic Cyst New England J Med 11 334 133
51 LOGAN P B and KLEINSASSER I J Surgery of the Pancreas Internat Al tr Surg 93 521 1951
52 MILLER G and RADEMAKER I End Results in Radical Operation for Carcinoma of the Periampullar Region of the Duodenum Ann Surg 13 13 1931
53 OUTERBRIDGE G Carcinoma of the Papilla of Vater Ann Surg 402 1913
54 WHIPPLE A O PARSONS W B and MULLIN C R Treatment of Carcinoma f the Ampulla of Vater Ann Surg 10 63 1935
55 TRIMBLE I R PARSONS J W and SHERMAN C I A One-stage Operation for the Cure of Carcinoma of the Ampulla of Vater and Head of the Pancreas Surg Gynec & Obst 3 711 1941
56 ORR T G Resection of the Duodenum and Head of the Pancreas for Carcinoma f the Ampulla Surg Gynec & Obst 3 240 1941
57 ——— Pancreaticoduodenectomy for Carcinoma of the Ampulla and Ampullary Region Surgery 18 144 1945
58 REYNOLDS J T and MARLOWE W Present Status of Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater and of the Head of the Pancreas J Int rnat Coll Surgeons 10 544 194
59 PEARSE H F A Simplified Anastomosis for Resection of the Duodenum and Head of the Pancreas Surg Gynec & Obst 5 333 1942
60 BRUNSCHWIG A Resection of Head of the Pancreas and Duodenum for Carcinoma Pancreaticoduodenectomy Surg Gynec & Obst 6 681 1937
61 CHILD C C Pancreaticojejunostomy and Other Problems Associated with the Surgical Management of Carcinoma Involving the Head of the Pancreas Ann Surg 119 845 1944
62 CHILD C G HOLSWADE C R McCLURE R D GORE A I and O NEILL E A Pancreaticoduodenectomy with Resection of the Portal Vein in the Macaca Mulatta Monkey and in Man Surg Gynec & Obst 4 31 1952
63 CATTELL R Resection of the Pancreas Surg Clin North America 3 1944
64 ——— B A Technique for Pancreatoduodenal Resection Surg Clin North America 8 761 1948
65 COLE W H and REYNOLDS J T Resection of the Duodenum and Head of the Pancreas for Primary Carcinoma f the Head f the Pancreas and Ampulla of Vater Surgery 18 133 1945
66 PERSON F C and GLENN F Pancreaticogastrostomy Ar h urg 39 530 1939
67 MILLER E M DOLBERTY M B WOLLAEGER E E and WAUGH J M Carcinoma in the Region of the Papilla f Vater Surg Gyne & Obst 9 12 1951
68 CATTELL P B and PYRTEK L J An Appraisal of Pancreatoduodenal Resection Ann Surg 1 840 1949
69 CHILD C G Radical One stage Pancreaticoduodenectomy Surgery 3 840 1949
70 WHIPPLE A O Tumor f the Pancreas and Ampull J Int nal Surg Gynec & Obst 3 112 1951
71 JUDD E and HOERNER M Surgical Treatment of Carcinoma f the Head of the Pancreas and Ampulla f Vater Arch Surg 31 33 1935
72 RANSOM H Carcinoma f the Body and Tail f the Pancreas Arch Surg 0 584 1935
73 ——— Carcinoma f the Juncture of the Bile Ducts Am J Surg 40 264 1938
74 WALTER W I COLE W H Surgical Lesions of the Pancreas Arch Surg 81 1941
75 WALTERS W and DELPRE I Jaundice Caused by Pancreatic Lesions Surg Gynec & Obst 6 2 1939
76 SALLICK M A and GARLOCK J H Obstructive Jaundice Due to Carcinoma of the Pancreas Surg 11 9 1942

77 Mikal S and Campbell A Carcinoma of the Pancreas Surgery 28 963 1950
78 Haunz L and Bagenstoss A H Carcinoma of Head of the Pancreas Effects of Obstruction of Ductal and Acinar System Arch Path 49 367 1950
79 Maxwell W Surgery of the Pancreas Australian & New Zealand J Surg 19 133 1950
80 Carlson R Problem of Diagnosis at Time of Operation in Tumors of Head of Pancreas Surgery 28 6 2 1950
81 Lrobstein J C Sachar L A and Rindskopf W Biopsies of Pancreatic Masses Surgery 2 356 1950
82 Elman R and Lieberman Z H The Pancreas Gastroenterology 21 24 1952
83 Greenler J J and Curtis C N Duodenal Diverticula Arch Surg 60 1011 1950
84 Sorkin S Z Blood Amylase Activity in Disease of Carbohydrate or Carbohydrate Metabolism and in Non diabetic Pancreatic Disease J Clin Investigation 2 329 1943
85 Innerfield I Angrist A and Benjamin J W Antithrombin Titer in Acute Pancreatitis Am J Med 12 24 1952
86 Cattell R B and Warren K W Surgery of the Pancreas Philadelphia Saunders 1953
87 McNeer G and Ewing J H Exfoliated Pancreatic Cancer Cells in Duodenal Drainage a Case Report Cancer 2 643 1949
88 Lemon H M and Byrnes W W Cancer of the Biliary Tract and Pancreas Diagnosis from Cytology of Duodenal Aspiration, J A M A 141 254 1949
89 Poppel M H Roentgen Manifestations of Pancreatic Disease Springfield Illinois Charles C Thomas 1951

Section V

APPENDIX

1 TECHNIC OF CHOLECYSTOGRAPHY

THE oral method is used exclusively at this hospital

On the day before the examination is to be made the patient has the usual breakfast lunch and a light fat free supper The dye* is given in tablet form each containing 0 5 gm Beginning at 7 00 P M 1 tablet is taken every five minutes with a glass of water for 6 doses

During this period no food of any kind is allowed Large amounts of water and fruit juices of all kinds are recommended

The next morning (the day of examination) no breakfast is allowed Liquids and sweetened fruit juices are permitted as desired The patient is instructed to report to the department of roentgenology about 9 00 A M

Following the oral administration of dye it is absorbed from the small intestine carried via the portal circulation to the liver and thence excreted in the bile The normal gall bladder is visualized twelve to eighteen hours after administration of the dye The dye is usually completely absorbed so that none remains in the large intestine Minor reactions are common These include nausea cramps diarrhea and sometimes burning on urination

Routinely roentgen exposures are taken with the patient in the prone and left oblique positions At least one exposure is made in the upright position This is useful not only for the determination of ptosis but in the demonstration of floating gall stones This has been demonstrated by many authors beginning with Sandstrom in 1929 The same procedure is useful in the demonstration of biliary sand or milk of lime Kirkland has also utilized the right decubitus position with a horizontal projection as an aid in separating gas shadows in the hepatic flexure from cholesterol stones At times a cleansing enema must be given for purposes of differential diagnosis since one of the most common sources of error consists in the confusing shadows produced by intestinal gas

Nonvisualization of the gall bladder is difficult to evaluate as explained on page 67 In order to eliminate the factor of lack of absorption of the dye by the intestinal tract as the reason for nonvisualization the patient is maintained on a fat free diet after the initial examination given another dose course of dye the evening of the same day and re examined the following morning This procedure is superior to giving an original double dose of dye and not repeating the examination on the following day

* Iodeikon

Following the initial examination the patient is given a meal high in fat (30 ml Bilevac* diluted with 30 ml water) to stimulate evacuation of the gall bladder as described on page 70 Further roentgen exposures are then made to demonstrate the contractility of the gall bladder Examiners differ as to the most advisable time for these exposures In our institution we routinely take a one- to two-hour exposure

Recently a new oral cholecystographic medium has been introduced This substance 3 (3 amino 2 4 6-triiodophenyl) 2-ethylpropanoic acid contains 66 68 per cent of organic iodine and is commercially available as Telepaque A high incidence of dense gall bladder shadows has been demonstrated with Telepaque optimum visualization being reached in ten to twelve hours after administration For adults 6 tablets (3 gm) are swallowed one at a time after an evening meal containing no fatty foods The tablets are preferably administered from ten to twelve hours before the scheduled examination Nothing should be taken by mouth after the tablets except ordinary amounts of water until bedtime The roentgenologic technic is the same as described above

In a number of instances the cystic and part of the common bile ducts have been visualized on the postcibal films if these are taken every fifteen minutes

2 TECHNIC FOR CHOLANGIOGRAPHY

Immediate (Operative) Cholangiography[1]

The region should be well exposed and the biliary structures dissected out thoroughly Incision into the gall bladder or bile ducts should be done after the roentgenogram has been taken

The most commonly employed and most useful method of immediate cholangiography is that in which the dye is injected through a needle into the common bile duct The needle usually 19 gauge connected to a 50-ml syringe by tubing and adapters is inserted into the common duct The identity of the duct is always confirmed by the aspiration of bile The ducts are then emptied of bile and 5 to 10 ml of iodopyracet is slowly administered with the anesthetist carefully checking the patient s pulse and blood pressure for signs of shock from overdistention A roentgenogram is then made while the patient is in respiratory arrest Two additional films are made each immediately after the injection of an additional 5 ml of contrast medium

Intra abdominal Choledochography

A 3 by 4 inch roentgen film in a plastic enclosed cardboard film holder is sterilized in 1 1 000 Zephiran chloride solution for thirty minutes Cholecystectomy and exploration of the bile ducts should include mobilization of the duodenum and head of the pancreas after the method of Kocher After the T tube has been inserted and the common bile duct sutured the sterile film holder is slipped into the space beneath the common bile duct and immobilized duodenum The watertightness of the sutured common duct is checked by saline injection through the T tube

* Picker X ray Corp

A self retaining retractor is inserted to hold the margins of the incision (rectus splitting transverse or paracostal) apart and the tube of a portable roentgen ray unit is centered over the curve of the duodenum at a distance of 30 inches from the surface of the operating table. After 15 to 20 ml of 35 per cent iodopyracet has been injected through the T tube a one and one half second exposure is made using 60 kv and 50 ma. No effort is made by the anesthetist to produce temporary apnea. The holder is removed and the film is developed immediately so that the status of the common bile duct may be known before the abdomen is closed.

Delayed Cholangiography

This is usually done ten to fourteen days after operation but may be performed as early as the seventh postoperative day.

Equipment 2 20-cc ampules of 35 per cent iodopyracet
1 sterile 20-cc syringe with adapter
2 sterile Kelly clamps
Sterile gloves
Sterile towel and gauze sponges
1 small emesis basin
Ampule of amyl nitrite
1 sterile 2-cc syringe
Stoppered vial of 1 1 000 epinephrine hydrochloride

The most satisfactory results are obtained when the patient is sent to the radiology department. After placing the patient on the roentgen ray table all dressings are removed. Sterile towels are placed over the incision and around the tube or fistulous opening. Residual bile in the tube is aspirated with the sterile syringe. The barrel of the 20-cc syringe is then attached to the tube and the latter is clamped immediately below the syringe. Iodopyracet is poured into the barrel and the clamp is removed permitting the contrast medium to enter slowly by gravity. When the biliary tract is filled and distended the patient will feel a dull pain in the epigastrium just to the right of the mid line with radiation directly backward. This indicates that sufficient contrast medium has been injected. The tube is clamped and roentgenograms are taken. If the developed films are not entirely satisfactory more iodopyracet may be introduced cautiously.

If the initial roentgenograms are satisfactory another roentgenogram is taken ten minutes later. The patient then inhales an ampule of amyl nitrite which should cause flushing of the face and a feeling of dizziness or faintness. Another roentgenogram is taken and repeated ten minutes later. In special cases when it is particularly desired to visualize the pancreatic or intrahepatic ducts it may be of value to administer morphine sulfate 16 mg (gr ¼) hypodermically one hour before cholangiography to cause spasm of the sphincter of Oddi and aid in securing a more complete filling of the biliary ducts.

Usually the anteroposterior and right oblique exposures are taken. At times a lateral exposure is useful. A Trendelenburg posture is not usually necessary but in difficult cases it has been used with success.

Gas bubbles are often difficult to differentiate from radiolucent stones The variable evanescent appearance of air bubbles aids in their diagnosis If doubt persists an exposure in the upright position is of considerable value since the air bubbles will tend to rise whereas calculi will not

In cases of choledochoduodenostomy cholangiography poses a special problem since the dye escapes into the duodenum without suitably filling the duct system Miller[3] has devised a T tube with a double lumen which overcomes this difficulty to some extent

BIBLIOGRAPHY

1 Carter R F and Gillette I Immediate Cholangiography J A M A *143* 951 1950

2 Slattery L R and Saypol G M Intra abdominal Choledochography Am J Surg *84* 229 1952

3 Miller H B A New Type of T Tube Am J Surg 79 750 1950

3 DIAGNOSTIC DUODENAL DRAINAGE

Drainage Equipment

The complete equipment for the drainage room is

Drainage table or bed with pillow sheet towel bathrobe
Drainage tube—Einhorn Lyon Levin Rehfuss Twiss or Matzner
Syringe bulb 30 cc or Luer 50 cc
8 widemouthed blood bottles (2 oz) with corks and labels
1 pus basin large
1 graduate 16 oz
1 drinking glass
1 vial Congo paper
8 oz 50 per cent solution magnesium sulfate
4 oz olive oil
2 safety pins
Vial tablets phenobarbital gr ½ (0 030 gm)
Vial tablets atropine sulfate gr 1/150 (0 0004 gm)
1 large ring stand with clamp and holder for specimen bottles
1 throat spray
1 oz solution cocaine HCl 2 per cent
1 oz silver Nucleinate 10 per cent

Routine Procedure—Unsterile*

Preliminary —The preliminary antispasmodic preparation of the patient is described on page 592

1 Patient to undress (women to remove corsets) and put on dressing gowns
2 Patient seated on bed or examining table and draped with sheet given pus basin to hold under chin

* Modified from B B V Lyon

3. Duodenal tube moistened with cold water or oil (mineral or olive oil).
4. Patient instructed to project tongue, forming groove down which tube can be slid.
5. Tube introduced; patient instructed to swallow like food and to *relax* as much as possible.
6. After initial tug of tube is felt (indicating the passage of the tube beyond the glottis) the tube may be pushed down until the two-ring mark is at the lips.
7. The gastric specimen is obtained at the two-ring mark (usual amount 30 to 60 ml.).
8. A gastric lavage is then done, using 100 ml. hot water at a time, repeating until return is clear.
9. The tube is then withdrawn nearly to the one-ring mark and *slowly* run through the stomach, with the patient lying on the right side. In an occasional patient the sitting position is preferable.
10. When duodenal intubation is done in the prone position, the tube is *run through to the three-ring mark in twenty-five minutes (timed)*, after which the bile is allowed to drain out by siphonage. The patient may be given a watch and told to swallow slowly at the rate of 1 in. every three minutes.
11. The nasal route may also be used, a Levin tube being moistened with oil and introduced through the nostril. When the tube reaches the back of the glottis the patient is instructed to swallow as the tube is slowly pushed downward.
12. The tube may be shown to be in the duodenum as described on page 55.
    a. If no bile is obtained, the tube should be withdrawn to the one-ring mark and slowly reintroduced. For extreme pylorospasm, relief may be obtained by the introduction through the tube or by hypodermic of atropine sulfate gr. 1/75 (0.0008 gm.).
    b. In cases where duodenal intubation is difficult because of gastric hyperacidity, *the introduction of ½ tsp. bicarbonate of* soda in 100 ml. *hot* water is indicated.
13. The duodenal or D specimen (A specimen of Lyon) (usually 30 to 60 ml.) is obtained without stimulation.
14. Stimulation is performed by introducing with the syringe 30 ml. equal parts of 50 per cent magnesium sulfate and hot water. This solution is allowed to remain in the duodenum for several minutes, *then allowed to drain out by siphonage*. The remaining magnesium sulfate is discarded; the M specimen is collected.
15. If no concentrated gall bladder bile is obtained following the magnesium sulfate stimulations, 1 oz. *warm* olive oil is introduced and allowed to remain in the duodenum *twenty minutes*.
16. The returning olive oil is then discarded as before and the O specimen collected.
17. Labeling specimens: Each bottle is marked with the *name of the* patient, the date, and the name of the specimen. The bottles are numbered consecutively as Gastric, D, M, O.

Sterile Precautions

For a sterile drainage the equipment and containers previously described are wrapped in a sheet and autoclaved

1 Patient to undress (removing corset or girdle) and put on dressing gown
2 Sterile set opened
3 Gargle prepared in sterile metal cup Silver Nucleinate 4 ml to ½ cup sterile water
4 Patient gargles throat is sprayed with Silver Nucleinate solution
5 Patient draped with sterile sheet pinning it around neck
6 Patient given sterile pus basin to hold under chin keeping hands under sheet
7 Operator pours a small amount of sterile water in graduate
8 Operator puts on sterile gloves or scrubs as for an operation
9 Duodenal tube moistened by dipping in sterile water of graduate
10 Duodenal tube is introduced and gastric specimen obtained as outlined under routine page 589
11 While the tube is passing through the stomach the syringe end of the tube is attached to the upper arm of the three way stopcock which is placed on the ring stand beside the table (See p 61)
12 After the three ring mark of the tube reaches the lips of the patient the position of the tip of the tube in the duodenum should be checked by the fluoroscope if no bile is obtained
13 Specimens of bile are then collected as described under routine page 589
14 A 5 ml sample of each specimen of bile is obtained in a sterile test tube through the three way stopcock flaming the tip of the stopcock and the mouth of the test tube
15 Test tubes and specimen bottles are labeled as before

Encapsulated Tube Method

Using Twiss Duodenal Tube —This method has been found to be more accurate in obtaining sterile cultures of duodenal bile With the encapsulated tube approximately 90 per cent of the duodenal bile specimens were found to agree with cultures obtained from the biliary tract at operation

The technic is similar to that described under sterile precautions (see above) with the following variations

Additional Equipment —1 Widemouthed bottle of ether containing keratin coated gelatine capsules and ¼ in sections of thin rubber tubing of similar size *

2 Pair of spreaders (these can be made from an old artery clamp) They are autoclaved in the sterile set

* The keratin coated capsule is prepared by selecting a gelatin medicine capsule of a size to fit closely over the duodenal bucket The ends are cut off with a razor blade leaving the double wall A solution of keratin dissolved in acetic acid is then applied in several coats with a medicine dropper only to the outside of the capsule

Procedure—1 Following opening of the sterile set the keratin coated capsule is placed with sterile precautions over the slotted bucket of the duodenal tube

2 The capsule is held in place by placing with the spreaders a rubber band over each end of the capsule being careful not to cover the central part (See p 61)

3 The tube is swallowed and passed through the stomach as before No gastric specimen is obtained however until the withdrawal of the tube at the conclusion of the drainage

4 After the three ring mark of the duodenal tube has reached the lips of the patient the capsule is dissolved in the duodenum by the introduction of hot sterile water by syringe

5 Whenever practicable the position of the duodenal tube should first be ascertained by fluoroscopic examination to be in the duodenum

Note—1 For hypersensitive throats a spray of 2 per cent cocaine hydrochloride is used before introducing the tube

2 For undue retching the patient is advised to breathe deeply and exhale forcibly For continued retching nervousness or excessive salivation 1/75 gr (0 0008 Gm) of atropine sulfate or phenobarbital gr ½ (0 030 Gm) or both are introduced through the syringe in a syringeful of *hot water*

Collection of Specimens for Cytologic Examination (pp 59 176 355 445)

Various methods have been used for the collection of specimens of duodenal bile If the specimens can be examined immediately a test tube of the duodenal content is collected and sent directly to the laboratory

The detailed technic for this procedure has been described by Lemon [1]

All tubing and equipment must be free of grease and oil No oil is used as a lubricant for the tube Slides must be chemically clean

The specimens are collected in chemically clean containers immersed in an ice bath The secretion is neutralized to pH 7 0 with 1 per cent sodium carbonate

Examination of the specimens is made within thirty minutes of their collection The secretion is centrifuged for thirty minutes and 1 to 4 drops of the sediment are smeared on each glass slide The slides are fixed immediately preferably in cold acetone or in equal parts of alcohol and ether The slides may be dipped twice into 1 per cent celloidin in acetone drying for a few seconds before staining by the Papanicolaou technic

Bowden and Papanicolaou[3] have devised the following procedure

Following introduction of the duodenal tube into the duodenum a specimen is collected over a period of twenty minutes in a container submerged in ice This specimen is immediately centrifuged for ten to fifteen minutes at 2 000 r p m One drop of the sediment is placed on each of several slides which have previously been prepared with albumin fixative or egg fixative This fixative is applied on the slide and allowed to dry before use

Following the application of the drop of sediment to the slide covered with albumin fixative a smear is made by applying the albumin-coated surface of another slide to the drop This smear is allowed to dry for a period of thirty to sixty seconds until the edge starts to dry The slides are then submerged in a bottle of equal parts of 95 per cent alcohol and ether and sent to the laboratory for examination

BIBLIOGRAPHY

1 LEMON H M The Clinical Value of Duodenal Drainage in the Diagnosis of Carcinoma of the Biliary Tract and Pancreas New York State J Med 51 18 1951
2 PAPANICOLAOU G N and TRAUT H L *Diagnosis of Uterine Cancer by the Vaginal Smear* New York Commonwealth Fund 1943
3 BOWDEN L and PAPANICOLAOU G N Personal communication

4 NEEDLE BIOPSY OF THE LIVER

By ALEXANDER S HONIG

Precautions —Before doing the biopsy certain precautions are necessary to safeguard the patient and to ensure the success of the procedure They are as follows

1 Bleeding coagulation and prothrombin time determination
2 Any bleeding tendencies should be corrected by administration of vitamin K
3 No biopsy should be performed if the prothrombin concentration is less than 50 per cent of normal by the Quick method
4 Because of the possibility of postpuncture bleeding the patient should be prepared to remain hospitalized for twenty four to forty-eight hours

Selection of Site for Biopsy —With appreciable hepatomegaly the subcostal or abdominal method is preferred The puncture is done in the midclavicular line below the right costal margin If the liver is not markedly *enlarged or if it is not palpable the biopsy should be done by* the transpleural method in the middle or anterior axillary line in the seventh to the tenth intercostal space depending upon the upper limit of liver dullness In case of a small liver some authors advocate peritoneoscopy and combine it with needle biopsy through the subcostal approach The needle is guided by direct vision through the peritoneoscope Peritoneoscopy is however a formidable procedure and requires the use of an operating room

Instruments —*The instrument which has been used for the needle biopsy* is usually a variation of the Iverson Roholm cannula or the Vim Silverman needle which does not require suction

The original Iverson Roholm needle is really a simple trocar consisting of a pointed stylet and a cannula 18 cm long and 2 mm wide The free edge of the cannula is quite sharp and notched so that the circumference forms a wavy line The needle is pushed through the skin and deeper tissues into the right lobe of the liver *The stylet is not removed until* the cannula has penetrated ½ in into the liver substance A plug of liver

tissue is then procured by pushing in the needle 4 to 5 cm farther A syringe is then connected to the cannula and suction is applied and maintained while the cannula is withdrawn Sherlock uses a cannula 15 cm long and 1 mm in diameter

Another modification is the Roth Turkle needle which consists of a stylet and a short outer cannula with a long beveled tip to facilitate puncture It also has a long hollow inner needle with small saw teeth at the end After puncture the inner needle is rotated slowly to cut out a cylinder of tissue The needle is withdrawn with the syringe attached to maintain negative pressure

The Vim-Silverman needle was originally devised for tumor biopsy and has become the most frequently used instrument for puncture biopsy of the liver A great advantage of this needle is that it does not require suction and therefore eliminates possible maceration of the biopsy specimen It is a 14 gauge needle 8 5 cm long with a stylet It has an inner needle 2 cm longer which is longitudinally split The specimen is cut by the inner needle A simplified technic eliminates the use of the stylet

Half an hour before the procedure an injection of morphine sulfate (0 015 gm) or 75 to 100 mg Demerol Hydrochloride (0 075 to 0 1 gm) is given to the patient The patient is placed in the supine position with the right arm behind the head and with the right side near the edge of the bed The area chosen is cleaned and draped with a sterile sheet with a central hole over the site of puncture The operator wears sterile glove In the intercostal approach the skin the intercostal muscles pleura diaphragm and surface of the liver are infiltrated with 2 per cent procaine solution About 10 cc are needed for the anesthesia A small incision is then made in the skin at the site of introduction The pleura is pierced while the patient is holding his breath in expiration

The Vim-Silverman needle is then inserted with the tip of the inner needle just visible at the tip of the outer one The patient is instructed to take a few deep breaths and finally to stop in full expiration The instrument is then inserted to a depth of about 6 cm penetrating approximately 2 to 3 cm into the liver The inner split needle is then inserted to its full length into the outer carrier needle advancing 2 cm farther into the substance of the liver A fragment of liver tissue is thereby trapped between the two prongs of the inner needle By rotating the inner split needle 180 degrees or more the liver tissue is cut off Now with the inner needle immobile the outer needle is advanced over the prongs of the inner needle for 2 cm The instrument is then withdrawn Speed in performing the puncture is essential During the biopsy which should not take longer than five to ten seconds the patient is in full expiration Continued respiration may cause a tear in the liver substance Half of the specimen is fixed in formaldehyde half is fixed in acetone for special studies

In the subcostal approach the technic with the Vim-Silverman needle is similar to the intercostal method Here however the patient can breathe freely

The size of the liver tissue which is obtained is usually small but as a rule it is large enough to be of diagnostic value In case of failure repeated attempts to obtain a specimen should be undertaken at the same

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time and at the same site This policy has reduced the number of unsuccessful biopsies to 5 to 6 per cent without increasing risk or discomfort to the patient

The aftereffects of needle biopsy are mild However the patient should be kept in bed for a day In the jaundiced patient 10 mg vitamin K are given parenterally immediately following the puncture biopsy Some patients experience pain at the site of puncture radiating to the right shoulder It is usually relieved by simple medication For the first twenty four hours the pulse is checked frequently and the patient is observed for signs of internal bleeding If indicated blood transfusion is given Excessive bleeding may require laparotomy

5 DUODENAL CONTENT TESTS FOR EXTERNAL PANCREATIC SECRETION

In spite of difficulties these tests can be done with a considerable degree of accuracy A prerequisite is that the importance of numerous details is properly understood and complied with

Duodenal Drainage Modified for Pancreatic Function Tests

Several essential modifications of the routine duodenal drainage (see p 588) are required especially quantitative collection of the discharge into the duodenum and preservation of the enzymatic activity

Need for Quantitative Drainage —Several duodenal pancreatic function tests determine not only the concentrations of pancreatic products in duodenal content but also the volume of the fluid output and the total output of bicarbonate and enzymes A prerequisite is that the secretion entering the duodenum be obtained quantitatively *i e* without loss into stomach and duodenum and purely *i e* without contamination by saliva and gastric juice

Possibility of Quantitative Duodenal Drainage [1,2,3]—Routine quantitative collection of duodenal content is possible when two special technics are employed (1) Simultaneous drainage from stomach and duodenum by means of double barreled tubes This prevents contamination by saliva and gastric juice (2) Continuous and constant suction so that no portion of the discharge into the duodenum escapes the collection

Factors influencing the quantitative efficiency of duodenal drainage are (1) Efficiency of the drainage tube as determined by caliber length and number as well as size of drainage openings (2) Amount and continuity of suction (3) Amount and rate of discharge into the duodenum Direct studies of these factors[1] showed that the efficiency of the available bilumen tubes plus suction of 6 cm mercury (90 cm water) are actually capable of preventing overflow of gastric juice to a great extent and to remove all amounts of duodenal content which may be expected under physiologic and pathologic conditions With this technic the removal follows the discharge into the duodenum immediately and is quantitative Direct proof that such drainage prevents loss of duodenal content down

into the jejunum was obtained by simultaneous drainage from the jejunum Figure 106 illustrates that during suction from the duodenum practically no duodenal content escaped into the jejunum whereas instantly after discontinuation of the suction bile stained duodenal content appeared in the jejunum

Equipment for Quantitative Duodenal Drainage — 1 *Double barreled (Bilumen) Drainage Tube for Simultaneous Drainage from the Stomach and Duodenum* — This clinic prefers the gastroduodenal tube of Moses Einhorn (manufactured by Clay Adams Co Inc New York) The caliber is conveniently small and the tube is completely rubber covered including the heavy ovoid tip It is available in oral and nasal types With curved scissors two additional drainage openings may be cut above the three original openings of both the duodenal and gastric barrels This extends the length of the drainage area and renders the drainage more independent of the inevitable variations of the position of the tube Care must be taken not to cut the membrane which separates the two barrels For orientation during drainage the oral end of the duodenal barrel is marked by a rubber band indelible ink etc (see Fig 105)

The insertion of the metal cannulas at the oral end must be checked to be airtight This check is done in the following way The insertion is placed under water The tube is clamped Air is blown through the two oral openings Leaks at this site result in a prompt formation of air bubbles suction The result is formation of foam and when ... suction is ... rapid loss of suction Foam may also develop from liberation of CO_2 from the duodenal content under the influence of negative pressure

A three barreled tube enables the use of a small inflated balloon at the tip of the tube This facilitates the passage of the duodenal barrel into the duodenum When the tip of the tube reaches the duodenal cap the balloon is inflated whereupon peristalsis immediately carries the tip of the tube through the duodenum to the ligament of Treitz

A portable electric suction pump with manometer is used (Fig 107) Together with a mercury trap automatically to ensure negative pressure Water suction pumps usually do not work with sufficient constancy If an electric pump is not available a Wangensteen apparatus may be used or two balloon syringes as shown in Figure 108 Bulbs and syringes must be tested to hold the suction The suction power of new bulbs may exceed 10 mm of mercury During the drainage the suction exerted by the bulbs must be watched constantly and reinstituted whenever necessary

2 *Freezing Mixture for Preservation of Enzymes During the Drainage* — Basin filled with crushed ice (not ice cubes) and a handful of table salt ... a small amount of water for chilling and preservation of enzymes during the test Some of the freezing mixture is filled in a flask (Fig 107) Thermometer for temperature below freezing

3 *Large Glass Pipettes* (10 ml)

4 *Timer*

5 *Instruments for Duodenal Drainage* (p 585)

6 *Calibrated cylinders* of 25 ml and 100 ml for the measurement of the ...

Stimulant Secretin insulin etc (see below) Syringe 5 ml for

secretin solution 1 ml for insulin 20 ml for blood specimen Needles gauge 20 Tourniquet Alcohol sponges

8 *Fluoroscope*

Make arrangements with the laboratory in advance so that the enzyme determination can be done without delay or the specimen be kept and preserved properly

Procedure of Quantitative Duodenal Drainage for Pancreatic Function Tests —(1) *Preparation of the Patient* —He is fasting for eight to twelve hours Drugs which affect the pancreatic secretion especially atropine and similar drugs must be avoided for twenty four hours They must not be used preparatory to the drainage or during it Nitroglycerin bromides or phenobarbital may be employed when required by antral or pyloric spasm

(2) *Passage of Gastroduodenal Tube* —The bilumen tube is passed as in routine drainage Any residue in the stomach is removed Fluoroscopic control of the passage through the stomach helps to accelerate the procedure The evaluation of the laboratory analysis depends entirely on the correct position of the tube Consequently *fluoroscopic check of the position of the tube is mandatory before beginning the collection* The position is correct when the tip of the tube is in the fourth or at the least the third portion of the duodenum Then the drainage openings of the duodenal barrel are in the second and third portions of the duodenum those of the gastric barrel are in the antral portion of the stomach The tube is now fixed in position by adhesive tape applied to the cheek

(3) *Suction* —The endings of both barrels are connected with suction bulbs or with the respective suction flasks of the suction apparatus The suction is set and maintained between minus 6 and 10 mm of mercury In addition constant suction from the mouth removes the saliva

(4) *Collecting and Recording* —This begins when the duodenal barrel is delivering clear golden yellow fluid and when the gastric juice is not bile stained In spite of correct position of the tube in the duodenum a stoppage of discharge may be noticed lasting twenty minutes or more [3, 36] Instillation of hot water occasionally breaks the stoppage The stomach may not secrete for even longer periods

The fractions of the collection are listed below

At the end of each collection period the rubber tubings to the suction flasks are clamped the suction bottle is opened and the inserted collecting vessel is quickly exchanged after which the suction is restored The volume and appearance (color turbidity) of each fraction of the duodenal and gastric content are recorded and the specimen is poured into properly labeled test tubes

(5) *Preservation of Enzymes* —The test tubes are immersed in the bowl with the freezing mixture The temperature of the latter is checked from time to time and ice is added if necessary Another means of preservation is to mix the sample thoroughly with equal amounts of pure glycerin [37]

(6) *Prestimulation Specimen* —The collection lasts for twenty minute and is labeled as the twenty to zero-minute specimen where zero indicate the time of stimulation If there is no discharge within forty or sixty

minutes after the correct position of the tube in the duodenum has been established fluoroscopically the collection of a prestimulation specimen is omitted In such cases the values after stimulation are compared only with the normal range of poststimulation values

(7) *Stimulation* —Humoral with secretin Vagal with mecholyl urecholin insulin Intestinal with olive oil See pp 436 and 442

(8) *Poststimulation Specimen* —After secretin injection the fractionation intervals are zero to ten ten to twenty twenty to forty forty to sixty and sixty to eighty minutes Many authors do not collect sixty to eighty minute specimens or combine the first two specimens

After injection of vagal stimulants *the fractionation intervals are zero* to ten ten to twenty and twenty to thirty minutes

In the combined secretin vagus test of Dreiling and Hollander specimens are collected for eighty minutes after the secretin injection Following the administration of vagal stimulus (insulin hypoglycemia) the duodenal output is collected for a second hour

For accurate fractionation a timer is recommended

(9) *Quantitative duodenal drainage demands uninterrupted presence and attention* of the person who does the drainage It is a full time job One must be sure that the time of the fractionation is kept accurately that there is no interruption of the suction change in the position of the tube or disturbance of the outflow

The drainage is undisturbed when the *gastric* tube delivers *colorless* fluid (or for certain periods no fluid at all) and when the *duodenal* tube *delivers clear and golden fluid which must flow in the normal poststimulation* period without prolonged interruptions

(10) *Disturbances of Drainage and Their Management* —The drainage can be disturbed by change of the position of the tube This may happen in spite of its fixation on the cheek and lip Relaxing and lengthening of an initially hypertonic and short stomach pulls the duodenal barrel back into the stomach or at least pulls the gastric barrel out of the prepyloric and *antral region so that antral secretion may escape gastric drainage and enter* the duodenum Such dislocation may also follow antiperistalsis associated with nausea retching and vomiting Reversely hunger contractions and shortening of an initially hypotonic and elongated stomach permit the tube and therewith the gastric barrel to slip down into the duodenum and the duodenal barrel into the jejunum in which case the duodenal discharge may be obtained via the gastric barrel but often contaminated with gastric juice

Outflow from the duodenal tube may become pale cloudy and acid This indicates (*a*) The duodenal tube has partly or entirely slipped back into the stomach (*b*) *Gushes of gastric secretion have escaped the gastric* suction Differentiation is obtained by fluoroscopy

Outflow from the gastric tube may become bile stained and in the presence of acid gastric secretion cloudy This indicates that (*a*) The gastric tube at least with one drainage opening has passed beyond the pylorus (*b*) Duodenal content has regurgitated into the stomach Differentiation again is obtained by fluoroscopy When the gastric secretion is anacid

or absent and when bile stained duodenal content has regurgitated into the stomach then the fluid obtained from the stomach may be yellow and clear as fluid from the duodenum simulating correct position of the tube

Such disturbances impair the quantitative efficiency of the drainage They must be recognized in time corrected as fast as possible and properly recorded The admixture of gastric juice can be recognized early in the glass connection between drainage and suction tubes Rapid exchange of the collecting vessel can save already evacuated uncontaminated material for examination of the concentrations

When the tube has advanced too far downward correction can be achieved by cautious pulling under fluoroscopic control When the duodenal barrel has slipped back into the stomach quantitative results for the entire test are no longer warranted Reintroduction as a rule causes a prolonged interruption Some diagnostic result is obtained in this case from the concentrations of pancreatic constituents in an uncontaminated specimen

There are rare cases which make quantitative and even qualitative evaluation of the drainage impossible because of hypermotility and/or hypersecretion of the stomach

(11) *Terminal Fluoroscopic Control* — A terminal check of the correct position of the tube is of great value for the reliability of the test

After termination of the prolonged drainage the patient is advised to take only some tea milk or soup and crackers and postpone a more substantial meal for one or two hours

BIBLIOGRAPHY FOR THE TECHNIC OF DUODENAL DRAINAGE

1 BERGER W V and OPPENHEIM F The Drainage Output from The Human Duodenum Extrinsic Factor Influencing Drainage Gastroenterol *1* 285 1943
2 ———— The Drainage Output from the Human Duodenum Physiological Factor Influencing Drainage Including a Method for Quantitative Duodenal Drainage Gastroenterol *1* 292 1943
3 BERGER W V The Interdigestive Discharge of Duodenal Content in Man Am J Digest Dis *11* 49 1944
4 LOPUSNIAK M S Experience with Secretin and Other Pancreatic Stimulant in the Study of Pancreatic Function Bockus H L *Postgraduate Gastroenterology* Philadelphia Saunders 1950 p 370

Methods of Analysis of Duodenal Content Normal Values*

The range of normal values differs widely owing to the methods of analysis employing different technic of digestion and enzyme determination The following figures are given for several methods employed in recent publications In part they are obtained by combination of various published values and personal experience For several reasons they are not final However marked deviations are diagnostic and border line values may support the diagnosis to a certain extent It is probable that the actual normal range can be narrowed in the future by elimination of errors

* For interpretation see p 435

in quantitative drainage by restriction to really normal persons instead of including patients who allegedly are not pancreatic but suffering from some abdominal disease and by better understanding of functional disorders Plotting of curves (Figs 109–114 120 129–132) aids the diagnostic evaluation As it stands today it seems advisable that each laboratory runs a series of normals with the methods used in order to check the results with those published in the literature Acceptance of a uniform standardized procedure of stimulation and analysis or at least a computation table for the values obtained by different methods would be an essential progress Adherence to the methods without modification is the prerequisite for the employment of the published normal values

1 *Fasting Test* (p 435) —The methods of determination are quoted in the following tests

Volume —0–30 ml per twenty minutes when continuous suction from stomach and duodenum is employed

Amylase concentration —5–1 (mean) Lagerloef unit or 0 34–1 7 gram maltose liberated from starch by 1 ml duodenal content (method of NORBY LAGERLOEF see test) 2–58 10 mg glucose liberated from starch by 0 001 ml duodenal content (method of FREE and MYER see test 5) —0 –?0 mg glucose liberated by 0 02 ml duodenal content (method of McCLURE WETMORE and REYNOLDS *see reference 6*) —*(300) 000–960 (00) gross Wohlgemuth units liberated from* starch by 1 ml duodenal content (method of WOHLGEMUTH see test 5)

Lipase (Tributyrin Esterase) concentration —5 5 26 ml 0 05 N sodium hydroxide necessary to neutralize the fatty acids liberated by 1 ml duodenal content (method of CRANDALL and CHERRY see test 3) —0–4 –10 ml 0 1 N sodium hydroxide by 0 1 ml duodenal content (method of FREE and MYER see test 5) —2–3 ml 0 1 N sodium hydroxide by 1 ml duodenal content (method of MYER and FINE described in reference 5) — 0 –2 4 ml 0 1 N sodium hydroxide by 0 0 ml duodenal content (method of McCLURE WETMORE and REYNOLDS oil splitting lipase see reference 6) — 0–60% splitting of Triolein (method of LEUBNER see test 6)

Protease (Trypsin) concentration —0 6–3 2 ml 0 1 N potassium hydroxide equivalent to amino acids liberated from casein by 1 ml duodenal content (method of WILLSTETTER and LAGERLOEF see test ?) —0 5–1 7 –4 5 mg non protein nitrogen liberated from casein by 0 02 ml duodenal content (method of FREE and MYER see test 5) —1 4 –3 5 mg non protein nitrogen liberated from casein by 0 02 ml duodenal content (method of McCLURE WETMORE and REYNOLDS see reference 6) —20 60% reduction of casein (method of LEUBNER see test C) —0 01 ml duodenal content or less liquefies 2 ml of 5 per cent gelatine (method of D ANDERSEN and M EARL see reference) —2 0–1042 units (method of CRO quoted in reference 4)

Bicarbonate —(0) 10–60 (80) mEq/l 200 00 Vol per cent CO (method see test 2)

Ict u Index —10–1 6 Meulengracht units

2 *Secretin Test of Agren G and Lagerloef H O* (p 456) —The methods are described in LAGERLOEF H O Pancreatic Function and Pancreatic Disease Studied by Means of Secretin New York The Macmillan Co 1942 *Amylase* Method of NORBY and LAGERLOEF saccharometric with sodium thiosulfate titration *Lipase* (oil splitting lipase) Method of RONA MICHAELIS and LAGERLOEF stalagmometric *Protease* Method of WILLSTETTER *et al* and LAGERLOEF titrimetric *Bicarbonate* titrimetric

3 *Volume* —(0) 0 00 ml *per 80 minutes* Subnormal below 0 ml low normal 0–90 ml supernormal above 1 00 ml —1 –5 0 ( ) ml kg 80 minutes Subnormal below 1 8 low normal 1 8 ? 2

Average

Enzyme concentration —Normal concentrating power is indicated in the combined fasting secretin test when at least one specimen prior or after the stimulation presents a concentration above the lower normal limit of the fasting test. See also test 3

Enzyme output per 80 minutes —

	Total Units	Total gram or ml	Units kg 80 Minutes
Amylase[1, 11]	240–1300 (2300)	44–166 gram maltose[2]	6–20
Lipase[1, 2]	7000–14000	(2400) 10 900–22 700 ml 0 05 N sodium hydroxide[2]	135–230
Protease (Trypsin)[2]	20–160	100–305 ml 0 1 N potassium hydroxide[2]	0 4–0 8

Bicarbonate maximum concentration —(60)–90–130 mEq/L acid combining power[1, 2] Subnormal below 70 low normal 70–90 —200–300 (600) vol %
Icteric Index —Drop to values between zero and 5 in at least one specimen or a fraction of it indicates normal filling function of the gall bladder. Absence of such drop suspect pathology of the gall bladder. In cases of absent or non functioning gall bladder the average minimal icterus index was 34

3 *Method of Test of Comfort M W and Osterberg A E* (p 442) —*Amylase* and *Protease* as in 2. *Lipase* CRANDALL L A JR and CHERRY I S Presence of an Olive Oil Splitting Lipase in the Blood of Patients with Multiple Sclerosis Proc Soc Exper Biol & Med *28* 572 1931 adapted for duodenal content (using a 1 10 dilution) by COMFORT M W PARKER R L and OSTERBERG A E The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen Am J Digest Dis *6* 249 1939 Acidimetric 24 hour method
Volume —95–13 ml 80 minutes (secretin test 118–282 ml)
Amylase maximum concentration —3 18–6 19 gram maltose liberated from starch by 1 ml duodenal content (secretin test 0 52 1 81 gram)
Lipase maximum concentration —82–200 ml 0 1 N butyric acid liberated by 1 ml duodenal content (secretin test 0–183 [425])
Protease maximum concentration —2 5–3 3 ml 0 1 N potassium hydroxide equivalent to aminoacid liberated from casein by 1 ml duodenal content (secretin test 1 0–3 7)
Bicarbonate maximum concentration —20–40 mEq/L maximum alkalinity pH 7 2–8 2 (secretin test pH 7 5–8 6) —See also the graphic presentation in reference 2 and the plotted values in Fig 104–116 and 120

4 *Secretin-Insulin Test of Dreiling D A and Hollander F* (p 442) —*Amylase* SOMOGYI M Micromethod for the Estimation of Diastase J Biol Chem *125* 399 1938 adapted for duodenal content *Protease* ANSON M L and MIRSKY A E Estimation of Pepsin with Hemoglobin J Gen Physiol *16* 59 1932 adapted for trypsin *Bicarbonate* VAN SLYKE D D and CULLEN G E Volumetric Method of Bicarbonate Determination in TODD J C and SANFORD A H Clinical Diagnosis by Laboratory Methods ed 11 Philadelphia Saunders 1950 p 412 VAN SLYKE D D and NEILL J M The determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement I J Biol Chem *61* 523 1924

Other Test of Free A H and Myers V C (p 442) —The methods are described in FREE A H and MYERS V C The Estimation of the Enzymes Amylase Protease and Lipase in Duodenal Content J Lab Clin Med *28* 138 1943 *Amylase* saccharometric colorimetric with picric acid reduction *Lipase* (tributyrin splitting) acidimetric *Protease* Determination of liberated NPN

Maximum in the individual test

Vol e —10–156 –23 ml per 60 minutes

Amyla e maxim concent t n —1 2–9 5C 18 2o mg gluc e equivalent per 0 001 ml duodenal content

L pa e (t ibi tyrin spl tting est a e) maxi m conce t atio —3 8) 1? 9o –34 8 ml 0 1 N sodium hydro ide per 0 1 ml duodenal content

Protema e axim m con er tratio —0 63–3 5 – 02 m non protein nitrogen p r 0 02 ml duodenal content

Ict s Ind x maxim m value —0–46 –1 54 As a rule the maximum is obtained in the 40 to 60 minute fr ction The above lor ler valu s are obtained by calcu lation from Table 1 in reference 3

(*Oil Test* of *Berg r W Hart an J ar I L i l r H* (p 442) —*Amylase* WOHLGE MUTH J New Method of Quantitative E tim ation f the Dia tatic Ferm nt Biochem Ztschr 9 1 1908 Mod fied by addition of sodium chloride (0 6%) and buffer (pH 6 8) GRADWOHL R B H Clinical Lab ratory Method of Diag is St Loui Mosby Co 1943 p 103 *Lipa e* LEUBNER H Method of Determi nation of Enzymes in Duodenal Content 3 Turbidimetric D terminati n of Lip ase Deutsche Zeitschr f Verd uungs u Stoffw chs elkr 1 155 1938 *P t ase* LEUBNER H Methods of Determination of Enzymes in Duodenal Content 2 Turbidimetric and Titrim tric Determination of Tryp i Dtsch Arch f Ver lauung kr 63 14 1938

The re ults are e pres d by maximal con entrations and or plotted as curves (Fig 126 130–132 See al o the r f r nce quoted or page 442)

Vol e —60 140 ml per 60 minutes fter the o t of flow

A yl e maxim concent t on — 160 3840 gross Wohlgemuth units

Lipa e x m co cent t on —34 to 80 per cent tri lein pl tti g

Prot axim co entrati —34 to 80 per cent r ducti n of c cin or 0 34–0 8 ml 0 0 N sodium hydroxide per 0 02 ml duodenal co t t

BIBLIOGRAPHY FOR NORMAL VALUES IN DUODENAL CONTENT

1 LAGERLOEF H O *Pancr t c Functic an I a e t e Di a e Stu l ed l y Means of S cretin* New York Macmillan 1942 AGREN G and LAGERLOEF H O The Pancr tic Secretion in Man After Intrav ous Admini tration of Secretin Acta Med Scandinav 90 1 1936

2 COMFORT M W and OSTERBERG A E Pan reatic Secretion in Man After Stimu l ti n with S cretin and Acetylbetamethyl holin Cli ri l Ar h Int Med 66 688 1940

3 FREE A H BEAM A J and MYER V C Studie of the Enzyme A tivities f Duoden l Content s a Mean of Evaluating Pancreatic Fu cti Gastro ent rol gy 1 188 1943

4 BERGER W HARTMAN J and LEUB ER H Method f Fractionati n of Duo den l C ntent in Sh rt Interval Wien Ar h f Inn e M d 5 I 211 1936 M TTI E M R *Cl i l I oc l f r Clin l Labo at r* Il ilad lphia Lea & Febiger 1936

5 MCCLURE C W WETMORE A S d REYNOLD L New Meth ds for E ti mating Enzymatic A tivitie f Duodenal Cont nt of Norm l Man Arch Int Med 27 06 1921 MCCLURE C W *F ctions I l t ftl I c a t ll Li e* New York Medical Authors Publishing Co 1933 LEUBNER H M th l of Det rmi nat n f Enzym in Duod nal C ntent 3 Turbidimetric D terminati n of Lipase Deut he Z itschr f V rd uu gs u l Stoffw l elkr 1 1 1938

6 – —— Meth l of Determin ti n of Enzym s in Du l r l C nt t 2 Tur b d m tri nd Titrim tr D t rmin ti of T p m Dt h Arch f V r l uung k 63 14 1938

N g

Th ngu l llect f du l l o t tu fi e minute interv l was l g n l by r lu l tul ely conta inati n with ga tric secr ti Aft r th ntroducti f the l uble tube techni th ollecti n p riod have l n ext nd l to 20 m nut s

9 ANDERSEN D H and EARL M V Method of Assaying Trypsin Suitable for Routine Use in Diagnosis of Congenital Pancreatic Deficiency Am J Dis Children 63 89 1942 ANDERSEN D H Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome Am J Dis Children 63 643 1942
10 DREILING D A and HOLLANDER F Studies in Pancreatic Function I Preliminary Series of Clinical Studies with the Secretin Test Gastroenterology 11 714 1948 Studies in Pancreatic Function II A Statistical Study of Pancreatic Secretion Following Secretin in Patients Without Pancreatic Disease Gastroenterology 1 620 1950
11 LOPUSNIAK M S Experience with Secretin and Other Pancreatic Stimulants in the Study of Pancreatic Function in BOCKUS H L *Post Graduate Gastroenterology* Philadelphia Saunders 1950
12 DIAMOND J S SIEGEL S A CALL M B and KARTEN S The Use of Secretin as a Clinical Test of Pancreatic Function Am J Digest Dis 6 366 1939 DIAMOND J S and SIEGEL S A The Secretin Test in the Diagnosis of Pancreatic Diseases with Report of 130 Tests Am J Digest Dis 7 435 1940
13 LAKE M Diagnostic Value of the Secretin Test Am J Med 3 18 1947
14 DORNBERGER G R COMFORT M W WOLLAEGER E E and POWER M H Pancreatic Function as Measured by Analysis of Duodenal Contents Before and After Stimulation with Secretin Gastroenterology 11 701 1948

6 SERUM ENZYME TESTS

Normal and Pathologic Values

Enzyme	*Method*	*Definition of Enzymatic Activity*	*Normal*	*Pathologic up to*
Amylase	Myer Free and Rosinski	mg maltose liberated from starch by 1 ml serum	1–2.5	9
		by 100 ml serum	100–250	900
	Somogyi[a]	mg maltose liberated from starch by 100 ml serum	50–200	800 (1600)
	Norby	mg maltose liberated from starch by 100 ml serum	100–335	4000
	Smith and Roe	1 unit equal 10 mg starch hydrolyzed by 100 ml serum	40–140 u	
Lipase oil splitting	Cherry and Crandall	ml 0 05 N fatty acid hydrolyzed by 1 ml serum	0–1 (2)	6 (12)
ester splitting (66	Goldstein and Roe[6]	ml 0 10 N fatty acids hydrolyzed by 100 ml serum	35–118	
Antithrombin	Innerfield Angrist and Benjamin	clotting time under specified conditions mean values at 1 minute incubation	16 4 seconds	27 6 seconds
		at 10 minutes incubation	55 seconds	318 seconds

BIBLIOGRAPHY

1 MYER V C FREE A H and ROSINSKI E E Studies on Animal Diastase 6 The Determination of Diastase (Amylase) in Blood J Biol Chem 154 39 1944

2 Somogyi M Micromethod for the Estimation of Diastase J Biol Chem 12 339 1938
3 Norby G Amylase in Blood and Urine in Lagerlöf H O Pancreatic Function and Pancreatic Disease Studied by Means of Secretin New York Macmillan Co 1942 p 23
4 Smith B W and Roe J H A Photometric Method for the Determination of Amylase in Blood and Urine with Use of the Starch Iodine Color J Biol Chem 1 9 63 1949
5 Cherry I S and Crandall L A Jr The Specificity of Pancreatic Lipase Its Appearance in the Blood After Pancreatic Injury Am J Physiol 100 266 1932
6 Goldstein N I and Roe J H Studies of Pancreatic Function I The Determination of Lipidolytic Enzymes of Blood Serum J Lab & Clin Med 5 1368 1943
7 Seligman A M Nachlas M M and Mollomo M C Colorimetric Determination of Lipase and Esterase in Dog's Serum Am J Physiol 1 9 337 1949
8 Innerfield I Angrist A and Benjamin J W Antithrombin Titer in Acute Pancreatitis Am J Med 1 24 1952

7 STANDARD TABLES OF HEIGHTS AND WEIGHTS

Weights in Pounds
(As Ordinarily Dressed)

Light face figures are 20 per cent under and over the average
(Reproduced by courtesy of the Medico-Actuarial Mortality Investigation)

(See Tables on page 604 and 605)

8 COMPOSITION OF FOODS*

Foods Highest in Carbohydrates

Foods Containing More Than 50 Per Cent Carbohydrate

Biscuits and crackers	Fruits canned fancy	Marshmallow
Bread and roll	Fruits dried	Milk chocolate
Cake	Honey	Molasses
Candy	Jams and jellies	Sugars and sirups
Cereal	Coconut dried	Zwieback
Condensed milk	Marmalades	

Foods Lowest in Carbohydrates

0 5 to 3 Per Cent Carbohydrate

Asparagus	Fish	Shad roe
Cauliflower	Lettuce	Shrimp
Chard	Lobster	Spinach
Cheddar cheese	Lean meat	Swiss cheese
Clams	Poultry	Turnip greens

* From Johnson H J Bridges' Dietetics for the Clinician 5th ed Philadelphia Lea & Febiger 1949

Heights		Weights According to Age Periods								
Feet	Inches	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to
4	11	[illegible] 111 133	94 117 140	98 122 146	100 125 150	102 127 152	104 130 156	106 132 1 8	106 133 160	107 134 161
5	0	90 113 13[illegible]	95 119 143	99 124 149	102 127 152	103 129 155	106 132 158	107 134 161	108 135 162	109 136 163
	1	92 115 138	[illegible] 121 145	101 126 1 1	103 129 1 5	10 131 157	10 134 161	109 136 163	110 137 164	110 138 166
	2	94 118 142	99 124 149	102 128 154	105 131 157	106 133 160	109 136 163	110 138 166	111 139 167	112 140 168
	3	97 121 14	102 127 1 2	105 131 1 7	107 134 161	109 136 163	111 139 167	113 141 169	114 142 1 0	114 143 1 2
	4	99 124 149	10 131 1	107 134 161	110 137 164	112 140 168	114 142 170	115 144 1 3	116 145 1 4	117 146 17
	5	102 128 154	108 135 162	110 138 166	113 141 169	115 144 173	117 146 1	118 148 1 8	119 149 1 9	120 150 180
	6	106 132 1 8	111 139 167	114 142 1 0	116 145 174	118 148 1 8	120 150 180	122 152 182	122 153 184	123 154 18
	7	109 136 163	114 142 1 0	117 146 1	119 149 1 9	122 152 182	123 154 18	12 156 18	126 157 188	126 158 190
	8	112 140 168	117 146 1	120 150 180	123 154 185	126 157 188	127 159 191	129 161 193	130 162 194	130 163 196
	9	11 144 173	1 0 150 180	1 3 154 185	126 158 190	130 162 194	131 164 197	133 166 199	134 167 200	134 168 02
	10	118 148 1 8	123 154 18	126 158 190	130 163 196	134 167 200	13 169 203	13 171 20	138 172 06	138 173 208
	11	122 153 184	126 158 190	130 163 196	134 168 202	138 172 206	140 175 210	142 177 12	142 178 214	143 179 215
6	0	12[illegible] 158 190	130 163 196	135 169 203	139 174 209	142 178 214	14 181 217	146 183 220	147 184 221	148 185 222
	1	130 163 196	134 168 202	140 175 210	144 180 216	14 184 221	1 0 187 224	1 2 190 228	153 191 229	154 192 230
	2	134 168 202	138 173 08	145 181 21	149 186 223	153 191 229	1 194 233	1 8 197 236	158 198 238	159 199 239
	3	138 173 208	142 178 214	150 187 224	1 4 192 230	158 197 23[illegible]	161 201 241	163 204 245	164 205 246	1[illegible] 206 247

WOMEN

Height: Feet	Height: Inches	Weight According to Age Period: 15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59
4	11	88 110 132	90 113 136	93 116 [illegible]	[illegible] 119 143	98 122 146	101 126 [illegible]	103 129 [illegible]	[illegible] 131 [illegible]	106 132 [illegible]
5	0	90 112 134	[illegible] 115 138	94 118 142	[illegible] 121 [illegible]	[illegible] 124 149	102 128 [illegible]	[illegible] 131 [illegible]	106 133 160	[illegible] 134 161
	1	91 114 137	94 117 140	96 120 144	98 123 148	101 126 [illegible]	104 130 [illegible]	106 133 160	108 135 162	110 137 164
	2	94 117 140	96 120 144	98 122 146	100 125 [illegible]	103 129 [illegible]	106 133 160	107 136 163	110 138 166	112 140 168
	3	[illegible] 120 144	98 123 148	100 125 [illegible]	102 128 154	106 132 158	109 136 163	111 139 167	113 141 169	114 143 [illegible]
	4	98 123 148	101 126 [illegible]	103 129 [illegible]	106 132 [illegible]	109 136 163	111 139 167	114 142 [illegible]	[illegible] 144 [illegible]	[illegible] 146 [illegible]
	5	102 126 151	103 129 [illegible]	106 132 [illegible]	109 136 163	112 140 168	114 143 [illegible]	117 146 [illegible]	118 148 [illegible]	120 150 180
	6	104 130 [illegible]	106 133 160	109 136 163	112 140 168	[illegible] 144 173	118 147 [illegible]	121 151 181	122 152 182	122 153 184
	7	107 134 161	110 137 164	112 140 168	[illegible] 144 173	118 148 178	121 151 181	124 155 186	126 157 168	126 158 190
	8	110 138 166	113 141 169	[illegible] 144 [illegible]	118 148 [illegible]	122 152 182	124 155 186	127 159 191	130 162 194	130 163 196
	9	113 141 [illegible]	116 145 [illegible]	118 148 [illegible]	122 152 182	[illegible] 156 187	127 159 191	130 163 [illegible]	133 166 199	134 167 200
	10	[illegible] 145 [illegible]	119 149 [illegible]	122 152 182	124 155 186	127 159 191	130 162 194	133 166 199	136 170 204	138 173 208
	11	120 150 180	122 153 184	124 155 186	126 158 190	130 162 194	133 166 199	136 170 204	139 174 209	142 177 212
6	0	124 155 186	126 157 188	127 159 191	130 162 194	132 165 198	135 169 203	139 173 208	142 177 212	146 182 218

Foods Negligible in Carbohydrates

- Bouillon
- Consommé
- Gelatine
- Mushrooms
- Cream cheese
- Sorrel
- Diabetic foods
- Vegetable marrow
- Vinegar
- Whitefish

Foods Highest in Cholesterol

- Bacon*
- Egg yolk*
- Fish roe*
- Kidney
- Liver*
- Sweetbreads*
- Butter
- Fish
- Lard
- Meats and poultry
- Oysters
- Suet

* Outstanding

Foods Lowest (Negligible) in Cholesterol

- Breadstuffs
- Egg white
- Cereals
- Fruit
- Sugars and sirups
- Vegetables
- Vegetable oils

Foods Highest in Fats

FOODS CONTAINING MORE THAN 20 PER CENT FAT

- Avocado
- Bacon
- Bone marrow
- Butter
- Catfish
- Caviar
- Cheese, whole milk
- Chocolate
- Cream
- Duck
- Egg yolk
- Fatty meats
- Fried food
- Goose
- Lard
- Margarine
- Meats, except very lean
- Nut butters or paste
- Nuts, except chestnut
- Oil, except mineral
- Pastry
- Potato chips
- Salad dressings
- Sardines in oil
- Sausage
- Suet
- Turkey
- Whole-milk powder

Foods Lowest (Negligible) in Fats

- Bouillon
- Cabbage
- Candy
- Cheese, skim milk
- Citrus fruit
- Cod
- Consommé
- Corn starch
- Cranberry sauce
- Currants, fresh
- Egg white
- Fig
- Fruit juice
- Gelatin, dry
- Greens, cooked
- Haddock
- Hominy
- Honey
- Jam
- Jellies
- Marmalade, orange
- Marshmallow
- Meat juice
- Melons
- Mushroom
- Okra
- Orchard fruit
- Peppers, green
- Pineapple
- Rhubarb
- Rice
- Root vegetable
- Salad greens, except cress and dandelion
- Squash
- String beans
- Sugars
- Sirups
- Tapioca
- Tomatoes
- Vinegar

9 DIETS FOR DISORDERS OF THE BILIARY TRACT AND LIVER

INDICATIONS FOR THE USE OF THE DIETS

Low lipid Diets

Diet 1

Composition	App CHO 120 P 90 F 60 Cal 1 200
Characteristics	Low cholesterol and fat low calorie
Indications	Fat intolerance eg tice-duct obstruction Active infection of the gall bladder or duct *Hypercholesterolemia cholelithiasis obesity*

Diet 2

Composition	App CHO 300 P 1[illegible]0 F [illegible]0 Cal 3 000
Characteristics	Low cholesterol and fat high calorie
Indications	As for Diet 1 except for malnutrition loss of weight

Antacid Diets

Diet 3A

Composition	App CHO 200 P 80 F 110 Cal 2 100
Characteristics	Bland antacid
Indications	Initial treatment in gastric hyperacidity [illegible] Duodenitis associated peptic ulcer Functional disturbances of the biliary tract with [illegible] and gastric hyperacidity

Diet 3B

Composition	App CHO 200 P [illegible]0 F 110 Cal [illegible]300
Characteristics	As for Diet 3A A maintenance diet for moderately severe case or to follow Diet 3A after improvement of symptom

High lipid Diets

Diet 4

Composition	App CHO 140 P 80 F 80 Cal 1 600
Characteristics	Relatively high cholesterol moderate fat low calorie
Indications	Functionally impaired or atonic gall bladder with biliary stasis Obesity

CONTRAINDICATIONS	Fat intolerance or cystic-duct obstruction Active infection of the biliary tract or liver damage Hypercholesterolemia or cholelithiasis

Diet 5

COMPOSITION	App CHO 300 P 140 F 140 Cal 3 000
CHARACTERISTICS	Relatively high cholesterol moderate fat high calorie
INDICATIONS	As in Diet 4 except for malnutrition loss of weight

Diet 6

COMPOSITION	App CHO 350 P 150 F 100 Cal 3 000
CHARACTERISTICS	High protein high carbohydrate moderate fat
INDICATIONS	Liver disease or liver damage as jaundice Hepatitis acute or chronic Cirrhosis biliary or portal Preoperative patients with severe weight loss or malnutrition

General Directions

MEALS	Meals should be small in amount and taken at the same time each day Large meals and overeating are detrimental All food should be chewed carefully
REST	A rest of ½ hour lying down should be taken after the noon or before the evening meal This allows the food to digest which is impossible with mental or physical work immediately following meals
BOWEL MOVEMENTS	An effort should be made to move the bowels every day after breakfast regardless of inclination If the bowels do not move regularly this fact should be reported
EXERCISE	A sufficient amount of outdoor exercise is essential for the proper functioning of the internal organs A brisk walk of at least twenty blocks should be taken every morning breathing deeply to stimulate the action of the gall bladder
WATER	At least 6 to 8 glasses of water should be taken daily A glass of water should be taken upon arising in the morning The remainder should be taken between meals rather than with meal
FOODS PROHIBITED	In general the following foods are best avoided
Fats	Pork fried foods gravies nuts olive
Roughage	Cabbage coleslaw cauliflower corn cucumbers celery bran
Irritants	Condiments spice sauces rich and highly seasoned foods hashed over spiced pickled and salted foods
Sweets	Pies cake candies chocolates and pastries
Stimulants	Alcohol and carbonated drinks coffee in moderation only

Diet 1

Low Cholesterol and Fat Low Calorie
(App CHO 300 P 120 F 60 Cal 3 000)

Breakfast

Fruit Juice OR Fruits	Orange grapefruit or pineapple juice 1 glass Stewed or canned apricots cherries peaches or pears (without syrup) ½ cup
Cereals	Oatmeal corn meal Pablum Puffed Rice or Puffed Wheat Triscuit ½ cup with milk and not more than ½ tsp sugar
Bread	Whole wheat or white bread ½ slice or ½ muffin or soft roll toasted with ½ square butter
Beverage	Cal C Tose milk (with top cream removed) Coffee coffee substitute or weak tea with milk and 1 lump or 1 tsp (level) sugar

Luncheon or Supper

Salad OR	Lettuce with cooked vegetables such as carrots string beans beets peas tomato or pear or pineapple Vinegar or lemon juice only
Sandwich	Whole wheat bread thinly buttered with plain cheese cream cheese or lean meat such as roast beef
Bread	With salad 1 slice whole-wheat or white bread preferably toasted thinly buttered
Beverage	Milk buttermilk 1 glass or weak tea with milk and 1 lump or 1 tsp (level) sugar

Dinner

Soup	Broth consommé or bouillon 1 small cup
Meat OR Fish	Chicken—roast broiled or boiled Beef—lean round sirloin or roast. Lamb—chops or roast Without visible fat Any lean fish not fried such as cod flounder haddock halibut perch whiting bass sole
Vegetables	Two cooked green or colored as for luncheon (prepared without butter)
Bread	As for luncheon
Beverage	Tea with saccharine

Avoid Foods high in cholesterol such as eggs and inner organs (liver kidney sweetbread brains) Foods high in fat such as avocado pork chocolate cream fried food lard greases thickened gravies butter peanut butter oil salad dressing duck goose nuts olives Foods high in starch such as bread potatoes macaroni spaghetti corn lima beans pies cakes candies pastries chocolate Other foods prohibited in the general directions

Note The diet is low in fats and therefore deficient in vitamins A and D For this reason there should be taken daily 1 multiple-vitamin capsule containing at least 5 000 units of vitamin A and 1 000 units of vitamin D

Diet 2

Low Cholesterol and Fat High Calorie
(App CHO 300 P 120 F 60 Cal 3 000)

Breakfast

Fruit Juice	Orange grapefruit pineapple or prune juice sweetened if desired
OR	
Fruits	Applesauce baked apple or sliced banana with cream and sugar
Cereals	Shredded Wheat (2 biscuits) Wheat flakes corn flake rice flakes Rice Krispies with milk and sugar Fruit may be added if desired Or cooked such as Ralston Cream of Wheat hominy boiled rice cream of barley or Farina with milk and sugar
Bread	Whole wheat or white bread toasted 2 slices with ½ square butter Jam jelly or marmalade if desired
Waffles	Waffles with sirup or honey may be substituted for cereal two or three times a week
Beverage	Coffee Sanka Kaffe Hag or Postum with 1 tb p milk and 2 lumps sugar Weak tea with milk and sugar or 1 glass milk

Luncheon or Supper

Juices	Tomato pineapple or vegetable juice without seasoning
OR Soup	Creamed soups made with milk or vegetable soups with barley okra rice macaroni spaghetti or vermicelli
Meat	Lean meat such as roast lamb roast beef or steak
Sandwich	Whole wheat or white bread toasted with roast beef, roast lamb ham plain cheese jelly etc
OR	
Salad	Lettuce with cooked carrot string beans beets peas tomato or pineapple With French dressing lemon juice or vinegar With crackers if desired
OR	
Vegetables	Potatoes—mashed baked or boiled Two green or colored vegetables such as carrots wax or string beans asparagus beets beet greens cauliflower (crown part only) young Lima beans peas lentils mushrooms okra squash turnips stewed tomatoes vegetable marrow
Bread	Whole wheat or white bread (2 slices) or rolls toasted with ½ square butter Jelly or jam if desired
Beverage	Skim milk 1 glass or weak tea with milk and 2 lumps sugar
Dessert	Stewed or canned fruit water ices gelatin or apple sauce

Dinner

Juice or Soups	As for luncheon
Meat	(Meat or fish should be taken once daily) Roast beef steak—tenderloin sirloin or round Lamb—chops or roast Chicken turkey chopped meat (Avoid fats and fried meats)
OR	
Fish	Bass blackfish bluefish cod flounder haddock halibut steak perch weakfish boiled salmon Served with lemon juice
Vegetables	One starch and two green or colored vegetables Potatoes—mashed baked or boiled Or macaroni spaghetti or rice With colored vegetables as listed for luncheon

Bread	As for luncheon
Dessert	As for luncheon
Beverage	Skim milk buttermilk 1 glass or weak tea with milk and 2 lumps sugar
10 A M	Cal C Tose or Hemo milk malted milk Cocomalt or Ovaltine Whenever possible 1 tbsp dextrose or lactose should be added With toast bread sticks or Zwieback
4 P M	As at 10 A M
10 P M	As at 10 A M

If there are digestive disturbances all salads raw fruits and raw vegetables should be omitted

Avoid Foods high in cholesterol such as eggs and inner organs (liver kidney sweetbreads brains) Foods high in fat such as avocado pork chocolate cream fried foods butter lard greases thickened gravies peanut butter oil salad dressings duck goose nuts olives Other foods prohibited in general directions

Note This diet is low in fats and therefore deficient in vitamins A and D For this reason it is recommended that there should be taken daily 1 multiple vitamin capsule containing at least 5 000 units of vitamin A and 1 000 units of vitamin D

Diet 3A

Bland Hyperacidity Diet With Intermediate Feedings
(App CHO 200 P 80 F 110 Cal 2 100)

Breakfast

Fruits	Canned or stewed apricots peaches or pears
Cereal	Cooked such as oatmeal Ralston Farina or Cream of Wheat Or prepared such as Puffed Rice or Puffed Wheat with 2 tbsp cream and ½ tsp sugar
Egg	One soft boiled or poached with portion butter as desired
Bread	White or whole wheat bread Zwieback or soft rolls toasted with 1 square butter
Beverage	Milk malted milk or Ovaltine Hemo or Cal C Tose may be added to milk for additional vitamins

Luncheon and Supper

Eggs or Chicken	One soft boiled coddled or poached with ½ square butter Other than fried
Vegetable	One potato—boiled baked or mashed with ½ square butter or 1 tbsp cream Or 1 cup rice steamed with cream or butter Two green or colored vegetables puréed or creamed such as carrots asparagus tips beets string or young Lima beans peas beet greens spinach squash turnips or avocado (2 tbsp) Puréed canned vegetables such as Clapp s or Gerber s are recommended
Bread	As for breakfast
Dessert	Stewed or canned fruits such as apricots peaches or pears (2 tbsp) Baked banana ice cream soufflés Junket Jell-O custard cornstarch or tapioca pudding Boiled rice with cream and ½ tsp sugar

Diet 2

Low Cholesterol and Fat High Calorie
(App CHO 300 P 120 F 60 Cal 3 000)

Breakfast

Fruit Juice OR	Orange grapefruit pineapple or prune juice sweetened if desired
Fruits	Applesauce baked apple or sliced banana with cream and sugar
Cereals	Shredded Wheat (2 biscuits) Wheat flakes corn flakes rice flake Rice Krispies with milk and sugar Fruit may be added if desired
	Or cooked such as Ralston Cream of Wheat hominy boiled rice cream of barley or Farina with milk and sugar
Bread	Whole wheat or white bread toasted 2 slices with ½ square butter Jam jelly or marmalade if desired
Waffles	Waffles with sirup or honey may be substituted for cereal two or three times a week
Beverage	Coffee Sanka Kaffe Hag or Postum with 1 tbsp milk and 2 lumps sugar Weak tea with milk and sugar or 1 glass milk

Luncheon or Supper

Juices	Tomato pineapple or vegetable juice without seasoning
OR Soups	Creamed soups made with milk or vegetable soups with barley okra rice macaroni spaghetti or vermicelli
Meat	Lean meat such as roast lamb roast beef or steak
Sandwich OR	Whole-wheat or white bread toasted with roast beef roast lamb ham plain cheese jelly etc
Salad OR	*Lettuce with cooked carrots string beans beets peas to*mato or pineapple With French dressing lemon juice or vinegar With crackers if desired
Vegetables	Potatoes—mashed baked or boiled Two green or colored vegetables such as carrots wax or string beans asparagu beets beet greens cauliflower (crown part only) young Lima beans peas lentils mushrooms okra squash turnips stewed tomatoes vegetable marrow
Bread	Whole wheat or white bread (2 slices) or rolls toasted with ½ square butter Jelly or jam if desired
Beverage	Skim milk 1 glass or weak tea with milk and 2 lumps sugar
Dessert	Stewed or canned fruit water ices gelatin or apple sauce

Dinner

Juice or Soups	As for luncheon
Meat OR	(Meat or fish should be taken once daily) Roast beef steak—tenderloin sirloin or round Lamb—chops or roast Chicken turkey chopped meat (Avoid fats and fried meats)
Fish	Bass blackfish bluefish cod flounder haddock halibut steak perch weakfish boiled salmon Served with lemon juice
Vegetables	One starch and two green or colored vegetables Potatoes—mashed baked or boiled Or macaroni spaghetti or rice With colored vegetables as listed for luncheon

Eggs	If eggs have not been taken at the other meals two soft-boiled or poached may be substituted for the meat or fish
Vegetables	One potato—mashed baked or boiled—or starches such as macaroni rice or spaghetti may be occasionally substituted With one to two green or colored vegetables such as asparagus beets carrots mushrooms okra pumpkin squash spinach wax beans tomatoes green peas vegetable marrow
Bread	Whole wheat or white bread 1 slice with 1 portion butter
Dessert	As for luncheon
Beverage	As for luncheon
10 A M	Cal C-Tose milk Cocomalt or buttermilk 1 glass With one egg if desired
4 P M	As at 10 A M
10 P M	As at 10 A M

Avoid Prune plums rhubarb All very sweet or very sour foods All rich and highly seasoned food All pickled and salted foods Condiments Salt and pepper at the table Red meats meat-stock soups bouillon Alcohol and carbonated drinks Tobacco If there are digestive disturbances all raw fruits and raw vegetables should be omitted

Diet 4

Moderate Cholesterol and Fat Low Calorie (App CHO 140 P 80 F 80 Cal 1600)

Breakfast

Fruit Juice OR Fruits	Orange grapefruit or pineapple juice 1 glass Stewed or canned apricots cherries applesauce peaches or pears Without syrup (½ cup)
Eggs OR	One soft-boiled with ½ square butter and a small pinch of salt
Cereals	Puffed Rice Puffed Wheat or Triscuit with milk and ½ tsp sugar May be substituted for egg two or three times a week
Bread	Whole wheat or white bread toasted ½ slice with ½ square butter
Beverage	Coffee tea or Postum 1 cup with 1 lump sugar and 1 tbsp cream

Luncheon or Supper

Juices OR Soup	Tomato or pineapple juice 1 small glass Bouillon consommé or clear broth 1 cup
Salad OR	Egg cooked carrots string beans beets peas tomato pear or pineapple with lemon juice or vinegar
Vegetable	Vegetable plate two green or colored vegetables with an egg if desired
Bread	Whole wheat or white bread toasted ½ slice with ½ square butter
Desserts	Stewed or canned fruits as for breakfast Custard Junket gelatin applesauce or water ice
Beverage	Whole milk 1 glass

Beverage	Milk buttermilk Ovaltine or Cocomalt 1 glass
10 A M	Milk malted milk buttermilk or Ovaltine Cal C Tose may be added to a glass of milk twice daily
2 P M	As at 10 A M
4 P M	As at 10 A M
10 P M	As at 10 A M
	Feedings every two hours are essential

Avoid Prune plums rhubarb All very sweet or very sour foods All rich and highly seasoned foods All pickled and salted foods Condiments Salt and pepper at the table Red meats meat stock soups bouillon Raw fruits raw vegetables salads Alcohol and carbonated drinks Tobacco and coffee

Note This restricted diet is temporary and is deficient in vitamins In order to correct this deficiency 1 multiple vitamin capsule containing at least 5 000 units of vitamin A and 1 000 units of vitamin D should be taken daily

Diet 3B

Bland Hyperacidity Maintenance Diet
(App CHO 200 P 120 F 110 Cal 2 300)

Breakfast (8 A M)

Fruits	Stewed or canned fruits applesauce
Cereals	Cooked cereal such as oatmeal Farina Cream of Wheat rice or rolled oats Prepared cereal such as Puffed Rice Puffed Wheat or corn flakes 1 cup with 2 tbsp cream and ½ tsp sugar
Egg	One soft boiled or poached with square butter and a small pinch of salt
Bread	Whole wheat or white bread 1 slice or soft roll toasted with portion butter
Beverage	Milk or malted milk 1 glass If there are no digestive symptoms 1 cup of Postum or weak tea with 1 tbsp cream and 1 lump sugar

Luncheon and Supper (12 noon or 6 P M)

Juices	Tomato or other vegetable juice (without seasoning)
Sandwich OR	White or whole-wheat bread preferably toasted with roast beef roast lamb plain cheese or jelly
Vegetable plate	One poached egg with two or three green or colored vegetables such as carrots beets asparagus tips mushrooms squash beans peas or vegetable marrow
Bread	As for breakfast
Dessert	Stewed or canned fruits such as pears apricots or peaches Baked apple (without skin) or applesauce Jell O gelatin custard Junket Puddings such as cornstarch rice tapioca Ice cream sherbets baked banana
Beverage	Milk malted milk Ovaltine or Cal C Tose 1 glass

Dinner (12 noon or 6 P M)

Juices	Tomato or other vegetable juice (without seasoning)
Meat OR Fish	(Meat or fish once daily) Chopped meat roast beef roast lamb lamb chops chicken other than fried Turkey (Fish should not be taken more than two or three times a week) Lean fish—baked boiled broiled or steamed such as cod flounder haddock halibut perch

Luncheon or Supper

Juices	Tomato or other vegetable juice (without added seasoning)
Soups	Creamed soups as desired
Sandwich	Whole wheat or white bread toasted with butter and egg
OR	chicken ham or plain cheese
Meat	Roast beef roast lamb lamb chops or steak
Vegetable	Potatoes—mashed or baked—with two green or colored vegetables
Dessert	As for dinner

Dinner

Juice	Tomato or other vegetable juice (without added seasoning)
Soups	As for luncheon
Meat	Turkey Beef—roast or broiled Steak—tenderloin sirloin
OR	or round Chopped meat lamb chops or roast lamb
Fish	*Baked boiled or broiled lean fish such as whitefish whiting* mackerel or bass may be taken two or three times a week
Vegetables	Two potatoes—mashed baked or broiled—with 1 square butter Rice macaroni or spaghetti with tomato sauce occasionally may be substituted if desired Two green or colored vegetables such as carrots beets beet greens lentils mushrooms okra peas Lima beans parsnips squash stewed tomatoes turnips vegetable marrow Avocado pear may be taken if desired with dressing
Bread	As for breakfast with jam or jelly if desired
Desserts	Apple tapioca Stewed or canned apricots plums pears or peaches Banana (baked or ripe) Irish or lemon blanc mange brown Betty bread cornstarch or rice pudding Prunes (stewed or purée'd) ice cream Cakes cup sponge or plain pound Custard American or Edam cheese In season very ripe fruits such as bananas apricots peaches or pears without skins or seed
Beverage	Tea with milk and 1 lump of sugar or milk one glass
10 A M	Milk 1 glass with 2 tbsp cream or an egg
4 P M	As at 10 A M or tea with cream and sugar Crackers or cakes
10 P M	Milk malted milk or Ovaltine 1 glass

Avoid Fried foods pork Thickened gravies sauces all rich and highly seasoned foods Condiments Pickled and smoked food Bran products Carbonated drinks Alcohol Pastries pie cocoa and chocolate

Note A moderate amount of food high in cholesterol and high in fats has been added to the diet in order to stimulate the emptying of the gall bladder The foods *high in cholesterol and fat* are eggs and inner organs such as liver kidney and sweetbreads It is important that these foods be used periodically as directed

Diet 6

HIGH CARBOHYDRATE HIGH PROTEIN MODERATE FAT AND HIGH CALORIE
(App CHO 350 P 150 F 100 Cal 3000)

Breakfast

Fruits	*Orange or grapefruit juice with 1 tsp sugar* Or bananas or stewed prunes with 1 tbsp sugar

Dinner

Juices or Soup	Tomato vegetable or pineapple juice 1 glass Bouillon consommé or clear broth 1 cup
Meats or Fish	Beef—round sirloin or roast Kidneys sweetbreads or brains are to be taken at least three times a week Lean fish (not fried) such as cod flounder haddock halibut perch whiting bass May be taken two or three times a week
Vegetables	Two green or colored vegetables (other than those prohibited) such as asparagus string beans wax beans beet greens lettuce mushrooms spinach squash tomatoes
Bread	As for luncheon
Dessert	Stewed or canned fruits such as pears peaches or apricots Custard Jell O gelatin or very ripe fruits without skins or seeds Baked apple applesauce
Beverage	Coffee (demitasse) weak tea or Postum with milk and 1 lump sugar
10 A M	Milk 1 glass
4 P M	Tea 1 cup with 1 tsp cream and 1 lump sugar
10 P M	Milk 1 glass

One of each of the above groups should be taken Those listed first are preferable the other foods may be taken occasionally for variety If there are digestive disturbances all salads raw fruits and raw vegetables should be omitted

Avoid Fried foods pork shellfish Thickened gravies sauces condiments salt and pepper at table Pickled smoked and salted foods Pastries pies cake candies chocolate cocoa Alcohol and carbonated drinks Smoking in moderation only

Note A moderate amount of food high in cholesterol and high in fats has been added to the diet in order to stimulate the emptying of the gall bladder The foods high in cholesterol and fat are eggs and inner organs such as liver kidney and sweetbreads It is important that these foods be used periodically as directed

Diet 5

RELATIVELY HIGH CHOLESTEROL AND FAT HIGH CALORIE
(App CHO 300 P 140 F 140 Cal 3 000)

Breakfast

Fruit Juices or Fruits	Orange grapefruit or pineapple juice with 2 tsp sugar Baked apple applesauce or banana with 2 tbsp cream and 1 tsp sugar
Eggs	Two soft-boiled or poached with 2 slices crisp bacon if desired
Cereal or	May be substituted for eggs two or three times a week Cooked such as rice oatmeal Cream of Wheat Wheatena or hominy Or prepared such as corn flakes rice flakes or Shredded Wheat with 2 tbsp cream and 1 tsp sugar
Waffles	May be substituted for eggs instead of cereal twice a week with sirup and butter
Bread	Whole wheat or white bread 2 slices or 2 soft rolls toasted with butter jam or marmalade if desired
Beverage	Cal C To e milk malted milk Ovaltine coffee or tea with 2 tbsp cream and 2 lumps sugar

Avoid Fats fried food grease oils pork veal thickened sauces gravies Liver kidneys sweetbreads brains Nuts dates olives condiments sauces Salted pickled and smoked foods Cucumbers Chocolate and cocoa

Note To supplement the protein intake 2 tb p a protein supplement preparation such as Melactin or Essenamine should be taken in milk once daily

Once daily 2 tbsp brewers yeast powder should be taken in a glass of milk if desired flavored with vanilla and nutmeg

At least 1 high potency multiple vitamin capsule (therapeutic formula) should be taken daily

The Low salt Diet

(Not Over 1 Gm Sodium Chloride)

SOURCES OF SODIUM TO BE AVOIDED

1 Salt both at the table and in cooking and preparing food
2 Commercially processed foods to which salt has been added These include
   - Smoked salt cured and other processed meats such as ham pork sausages corned beef salt fish canned meats and fish bouillon cubes and meat extracts
   - Cheese
   - Pickled and spiced products such as olives pickles catchup sauces salad dressings and prepared mustard
   - Canned vegetables soups meats and fish
   - Salted butter margarine and other salted fats (Four squares only of sweet butter or margarine allowed daily)
   - Ordinary bakery goods and crackers
   - Many prepared cereals
   - All other salted foods such as pretzels potato chips popcorn salted nuts and most candies and candy bars
3 Foods with a high natural salt content meat eggs and milk Meat and eggs may be eaten in limited amounts Milk should be replaced by Lonalac
4 Soda products such as baking soda (sodium bicarbonate) and baking powder and self rising flours including pancake biscuit muffin and cake mixes also various laxatives and other remedies containing salts
5 Medicines containing salt or bicarbonate of soda

Foods	*Permitted*	*Forbidden*
Dairy Products	One egg daily Sweet butter Cream Salt free cottage cheese	All other cheeses salted butter
Vegetables	All fresh vegetables except those forbidden	Fresh avocado beet carrot celery chard dandelion Lima bean onion parsnip rhubarb spinach olive Canned vegetables Pickles

Cereals	Oatmeal, rice, Cream of Wheat, Wheatena, hominy. Or prepared cereal with 2 tbsp. cream and 1 tsp. sugar
Eggs	One if desired, with ½ pat butter. With 2 slices bacon
Meat	Chops or steak may be taken instead of eggs and bacon
Waffles	Waffles with sirup and 1 square butter may be substituted for cereals two or three times a week
Bread	Whole wheat or white bread, 2 slices, toasted, with butter, jam, jelly, or marmalade
Beverage	Tea, Sanka, or coffee with 1 lump of sugar and 1 tbsp. milk

Luncheon or Supper

Juices	Tomato or vegetable juice (without added seasoning)
Meat	Lean meat, such as roast beef, roast lamb, or steak, or lean fish other than mackerel or swordfish, should be taken twice daily
Sandwiches OR	Two sandwiches, toasted whole wheat or white bread, with cream or plain cheese, eggs, jelly, jam, or meat
Vegetables	A vegetable plate with a poached egg may be taken two or three times a week. Mashed or baked potatoes may be taken with ½ square butter
Salad	Lettuce with cooked vegetables or stewed or canned fruits may be taken, such as peas, carrots, string beans, peaches, or pears. With mineral-oil salad dressing, cream cheese, or lemon juice
Bread	As for breakfast
Dessert	Stewed or canned fruits. Cornstarch, rice, bread, or tapioca pudding. Baked apple or applesauce. Baked or fresh banana with milk and sugar. Irish or lemon blancmange. Cakes, cup, plain, or sponge. Custards. Jell-O, gelatin. Junket
Beverage	Tea, 1 cup, with 1 lump sugar

Dinner

Juices	Tomato or other vegetable juice (without added seasoning)
Soups	Bouillon, consommé, or broth with rice, barley, macaroni, or noodles
Meats	A liberal portion of lean meat is to be included in two meals each day
Vegetables	Potatoes—mashed, baked, or boiled—with ½ square butter. Or macaroni, rice, or spaghetti with ½ square butter or 1 tbsp. cream. With two green or colored vegetables, such as carrots, asparagus, beets, beet greens, peas, pumpkin, string or wax beans, stewed tomatoes, turnips, vegetable marrow
Bread	As for breakfast
Desserts	As for luncheon
Beverage	As for luncheon
10 A.M.	Milk, malted milk, or Cocomalt, 1 glass. To milk may be added 2 tsp. Hemo or Cal-C-Tose. To be taken with Zwieback crackers, toast, or arrowroot crackers
4 P.M.	As at 10 A.M.
10 P.M.	As at 10 A.M.

With digestive symptoms, all salad, raw fruits, and raw vegetables should be omitted.

Avoid Fats fried foods greases oils pork veal thickened sauces gravies Liver kidneys sweetbreads brains Nut dates olives condiments sauces Salted pickled and smoked foods Cucumbers Chocolate and cocoa

Note To supplement the protein intake 2 tbsp a protein supplement preparation such as Melactin or E enamine should be taken in milk once daily

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SOURCES OF SODIUM TO BE AVOIDED

1 Salt both at the table and in cooking and preparing food
2 Commercially processed foods to which salt has been added These include
   Smoked salt-cured and other processed meats such as ham pork sausages corned beef salt fish canned meats and fish bouillon cubes and meat extracts
   Cheese
   Pickled and spiced products such as olives pickle catchup sauces salad dressings and prepared mustard
   Canned vegetables soups meats and fish
   Salted butter margarine and other salted fats (Four squares only of sweet butter or margarine allowed daily)
   Ordinary bakery goods and crackers
   Many prepared cereals
   All other salted foods such as pretzels potato chips popcorn salted nuts and most candies and candy bars
3 Foods with a high natural salt content meat eggs and milk Meat and eggs may be eaten in limited amounts Milk should be replaced by Lonalac
4 Soda products such as baking soda (sodium bicarbonate) and baking powder and self rising flours including pancake biscuit muffin and cake mixes also various laxatives and other remedies containing salts
5 Medicines containing salt or bicarbonate of soda

Foods	*Permitted*	*Forbidden*
Dairy Products	One egg daily Sweet butter Cream Salt free cottage cheese	All other cheeses salted butter
Vegetables	All fresh vegetables except those forbidden	Fresh avocado beets carrots celery chard dandelion Lima beans onion parsnips rhubarb spinach olives Canned vegetables Pickles

Cereals	Oatmeal rice Cream of Wheat Wheatena hominy Or prepared cereal with 2 tbsp cream and 1 tsp sugar
Eggs	One if desired with ½ pat butter With 2 slices bacon
Meat	Chops or steak may be taken instead of eggs and bacon
Waffles	Waffles with sirup and 1 square butter may be substituted for cereals two or three times a week
Bread	Whole-wheat or white bread 2 slices toasted with butter jam jelly or marmalade
Beverage	Tea Sanka or coffee with 1 lump of sugar and 1 tbsp milk

Luncheon or Supper

Juices	Tomato or vegetable juice (without added seasoning)
Meat	Lean meat such as roast beef roast lamb or steak or lean fish other than mackerel or swordfish should be taken twice daily
Sandwiches OR	Two sandwiches toasted whole wheat or white bread with cream or plain cheese eggs jelly jam or meat
Vegetables	A vegetable plate with a poached egg may be taken two or three times a week Mashed or baked potatoes may be taken with ½ square butter
Salads	Lettuce with cooked vegetables or stewed or canned fruits may be taken such as peas carrots string beans, peaches or pears With mineral-oil salad dressing cream cheese or lemon juice
Bread	As for breakfast
Dessert	Stewed or canned fruits Cornstarch rice bread or tapioca pudding Baked apple or applesauce Baked or fresh banana with milk and sugar Irish or lemon blancmange Cakes cup plain or sponge Custards Jell O gelatin Junket
Beverage	Tea 1 cup with 1 lump sugar

Dinner

Juices	Tomato or other vegetable juice (without added seasoning)
Soup	Bouillon consommé or broth with rice barley macaroni or noodles
Meats	A liberal portion of lean meat is to be included in two meals each day
Vegetables	Potatoes—mashed baked or boiled—with ½ square butter Or macaroni rice or spaghetti with ½ square butter or 1 tbsp cream With two green or colored vegetables such as carrots asparagus beets beet greens peas pumpkin string or wax beans stewed tomatoes turnip vegetable marrow
Bread	As for breakfast
Desserts	As for luncheon
Beverage	As for luncheon
10 A M	Milk malted milk or Cocomalt 1 glass To milk may be added 2 tsp Hemo or Cal C Tose To be taken with Zwieback crackers toast or arrowroot crackers
4 P M	As at 10 A M
10 P M	As at 10 A M
	With digestive symptoms all salads raw fruits and raw vegetables should be omitted

Preparation of Liquid Lonalac

(For Use as Milk)

Place 1¼ cups lukewarm water in a widemouthed pan. Put a scant ¾ cup Lonalac powder on the surface of the water and beat it in gradually with an egg beater. When it is well mixed and there are no more lumps, add another 1¼ cups lukewarm water and blend thoroughly. Place the mixture in a covered jar in the refrigerator as soon as it has cooled to room temperature, for liquid Lonalac requires the same care as milk. The mixture foams as it is being mixed, but if the following day's supply is mixed in the evening and refrigerated overnight, the foam will largely disappear. If during refrigeration some powdery material should settle out, gently invert the container several times. Lonalac prepared in this way is used in cooking or as a beverage just as milk is used.

Preparation of Double strength Lonalac

(For Use as Cream)

Start as directed above. After the Lonalac powder has been mixed with the 1¼ cups water, pour off ½ cup. Then add only ¾ cup water to the rest of the original mixture. Yield: ½ cup double strength, 1½ cups single strength. The double-strength mixture may be used with coffee, cereals, and fruits or in any way in which cream is used.

Tube Feedings*

Tube feedings may be given as gastric or duodenal feedings. With gastric feedings the patient should have the head elevated and the body at an angle of 45 degrees. Care must be taken not to permit regurgitation of liquid into the trachea. In patients who are vomiting, duodenal feedings of liquids with a Levin-type tube may be a preferable procedure.

Foods for Duodenal tube Feeding

Acid milk	Eggs (raw)	Malted milk
Albumen fruit juices	Fruit juices	Milk, cow's or goat's
Buttermilk	Honey	Olive oil
Cereal gruels	Karo	Ovaltine
Cream	Lactose (10 to 20 per cent solution)	Sugar
Dextri-Maltose		Vegetable purées

Tube feeding Schedule

The following diet contains approximately 90 gm. protein and 2,800 cal. The feedings should be warmed before being given. Following each feeding the tube should be washed out with a few ounces of water.

* From BRIDGES: *Dietetics for the Clinician*, 5th ed., Philadelphia, Lea & Febiger.

Fruits	Fresh and canned fruits	Raisins and dates
Desserts	Puddings gelatin desserts and fruit	Bakery bought cakes and cookies
Condiments and Flavorings	All pice cinnamon garlic ginger lemon extract nutmeg paprika pepper peppermint extract sage thyme vanilla extract vinegar	All easoning agents except those permitted Relishes catchup celery salt onion salt and sauces
Fats and Oil	All fats and oils such as lard Spry and Crisco	Salted butter oleomargarine prepared salad dressings
Miscellaneous Food	Homemade soups prepared without salt unsalted nut unsalted popcorn jams jellie marmalade honey	Ice cream canned soups bouillon cubes gravies
Salt Substitutes	Neocurtasal	Curtasal
Beverages	*Dialyzed* milk or *Lonalac* (Mead Johnson) Tea coffee Postum fruit juices chocolate Coca Cola or ginger ale	Tomato juice milk beer mineral waters
Meat and Fish	Fresh meat and poultry fresh water fish	All salted or smoked meats such as bacon ham, canned meats kidneys All sea foods such as oysters lobster shrimp etc Smoked or canned fish
Bread	Salt free bread Goodman matzohs Homemade biscuits and cakes in which baking soda or salt was not used in preparation	Bread Bakery products
Cereals and Substitutes	Cooked cereals prepared without salt such as oatmeal corn meal Farina Wheatena Instant Ralston Maltex Dry cereals allowed Puffed Rice Puffed Wheat and Shredded Wheat Goodman spaghetti noodle vermicelli and macaroni Rice	All dry cereals except those permitted

SAMPLE MENU

Breakfast	*Dinner*	*Supper*
Fruit Cereal with low sodium milk and sugar Egg Salt free toast sweet butter Coffee Low sodium milk	Roast lamb Rice Peas Salt-free bread sweet butter Salt-free dessert Beverage	Cottage cheese Baked potato Salt free bread sweet butter Applesauce Beverage

NOON

of a pound of finely chopped re t beef (raw weight) lightly broiled *so that the interior remains uncooked* In addition ⅛ of a pound of mashed potato (½ lb potato ½ glass milk 1 square of butter salted to taste)

AFTERNOON

Same as morning

EVENING

Same as forenoon

DIRECTIONS On the first morning take a cleansing enema and the red capsule marked medicine 1 Then adhere strictly to above diet for *three days* On the morning of the fourth day take 3 teaspoonfuls of medicine marked 2 Collect the stool beginning with the first red stool and terminating with the last specimen before the charcoal appears Deliver all specimens or—when so directed—any two specimens between the red and black specimen During this period don t take medicines influencing the digestion such as pancreatin or laxatives

FOR THE PHYSICIAN ℞ Carmine One capsule Label medicine 1
Sig Take this capsule on the first morning before breakfast
℞ Carb veget 15 gram
Mucilag gummi arab 15 gram
Aqu menth pip 60 ml
Label medicine 2 Sig Take three teaspoonful on the fourth day before breakfast

Above diet yields approximately carbohydrate 180 gram fat 132 gram protein 100 gram Calories 2325 Average daily weight of dried feces for the three-day period 55 gram range 45–62 In external pancreatic deficiency 3–4 times this amount When the average daily weight exceeds 300 gram complete obstruction of the pancreatic ducts is present (Pratt)

10 Intravenous Cholangiography

Following is the procedure used for the intravenous cholangiogram

1 No breakfast
2 A flat plate of the abdomen is taken
3 A test dose of 1 ml of Cholografin is given intravenously
4 The blood pressure and pulse are taken before and after the injection
5 After an interval of 10 to 20 minutes if there is no reaction to the test dose 20 ml of Cholografin is given intravenously slowly over a period of 5 minutes With heavy individuals or in cases where an intense shadow is desired 40 ml can be given over a period of 10 minutes
6 Plates are taken at intervals of 20 and 40 minutes If the bile ducts are not visualized an additional plate is taken at 60 minutes
7 If desired a hypodermic injection of morphine sulphate 10 mgs (gr ⅙) may be given subcutaneously preceding the injection of the Cholografin This is not necessary in most cases for visualization of the bile ducts

11 Oral Cholangiography*

The following instructions are used for patients having post-cholecystectomy symptoms and for those having no visualizations of the gall bladder on cholecystographic examination

* Investigations have not been completed as to the details of this procedure. Present evidence suggests that a fat-free breakfast at 7 A M may facilitate the absorption of the dye and increase the amount excreted in the bile

Feedings

8 A M	Milk 8 oz Cream 2 oz Cereal gruel 4 oz	6 P M	Milk 8 oz Cream 2 oz Puréed vegetable or fruit 4 oz
10 A M	Milk 8 oz Orange juice 4 oz Egg 1	8 P M	Milk 12 oz Cream 2 oz Cocoa paste ½ oz
12 NOON	Milk 8 oz Cream 2 oz Puréed vegetable 4 oz Pinch of salt	10 P M	Milk 8 oz Cream 2 oz Cereal gruel 4 oz
2 P M	Milk 8 oz Cream 2 oz Cereal gruel 4 oz	2 A M	Milk 8 oz Orange juice 4 oz Egg 1

GASTRIC TUBE FEEDING FORMULA

Skim milk	1500 cc
Eggs	3
Glyco e Dyno	120 gm
Protinal	100 gm
Ground Liver	200 gm
Water to	2400 cc
Content CHO 210 P 200 F 500 Calories 2000	

From Seng taken R W and Blakemore A H Balloon Tamponade for the Control of Hemorrhage from Esophageal Varices Ann Surg *131* 781 1950

If there is an intolerance to fats the cream should be omitted and skim milk powder added

Nasal Tube Feedings

A powder which with the addition of water makes a solution suitable for all types of disorders requiring tube feeding with the advantage and convenience of administration with a small plastic nasal tube is available as Sustagen (Mead Johnson) This powder will supply all necessary nutritional requirements including vitamins and minerals

Test Diet for Enteral Assimilation in Pancreatic Disease (p 445)

Modified Test Diet of Adolf Schmidt for Gross and Microscopic Examination of the Feces

MORNINGS
1 pint of milk
2 oz toast

FORENOON
Oatmeal gruel (2 oz rolled oats 1 square of butter ½ pint milk ½ pint water and 1 egg Salt to taste and strain)

INDEX

A

1 No fluid after 8 P M the day preceding the examination
2 No breakfast
3 Beginning at 7 A M the day of the examination, take 6 Telepaque tablets with a glass of hot water Repeat at 7.30 A M
4 One large glass (6 oz) of water should be taken with the tablets
5 Paregoric is taken with a swallow of water 2 teaspoonfuls at 10 A M
6 Films are taken at 11 A M at 12 and at 1 o clock
7 No food or fluid is to be taken until completion of test
8 After the 1 o clock film a fat meal is given to empty the bile ducts The final film is taken 30 minutes later

B

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M

T